



FAST DISSOLVING ORAL FILMS: AN INNOVATIVE DRUG DELIVERY SYSTEM

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Abstract:

The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. The most popular oral solid dosage forms are tablets and capsules. Many patients find it difficult to swallow tablets and hard gelatin capsules particularly pediatric and geriatric patients and do not take their medicines as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. In some cases such as motion sickness, sudden episode of allergic attack or coughing ,fear of choking and an unavailability of water, the swallowing of tablet or capsules may become difficult. To overcome these difficulties, several fast-dissolving drug delivery systems have been developed.¹ Oral fast dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which rapidly dissolves on tongue or buccal cavity. The film overcome the danger/fear of choking .An ideal film should have the properties like pleasant taste , high stability, ease of handling and administration, no water necessary for application.

Key words: Fast dissolving film, dysphagia, pediatric, hydrophilic polymers.

Introduction:

The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.

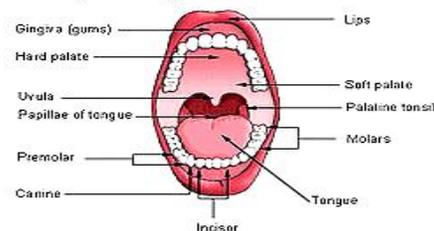
Oral fast dissolving film (FDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The need for non-invasive delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

Approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. A new oral fast dissolving dosage form such as the fast dissolving tablet or fast dissolving film has been developed which offers the combined advantages of ease of dosing and

convenience of dosing in the absence of water or fluid. Most of the existing fast-dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth within a few seconds or minutes, without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. The film overcome the danger/fear of choking¹.The development of a fast-dissolving film also provides an opportunity for a line extension in the market place; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form.^{2,5-9}

Overview of Oral Mucosa^{2,18,20}:

Mouth (Oral Cavity)



Drug delivery via the oral mucosa is a promising route, when one wishes to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. Thus, there is a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating strip, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids. However, in addition to formulation considerations, the properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intraoral administration. The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer.

Criteria for Fast Dissolving Film^{2,3}:

- Fast dissolving film should
- ✓ Have a pleasant mouth feel.
- ✓ Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- ✓ Be compatible with taste masking
- ✓ Leave minimum or no residue in the mouth after oral administration.
- ✓ Exhibit low sensitivity to environmental conditions such as temperature and humidity.
- ✓ Allow the manufacture of the tablet using conventional processing and packaging equipments at low cost

Advantages of FDF^{2,4,5}:

- ✓ Ease of administration to pediatric, geriatric, bedridden patients and psychiatric patients who refuse to swallow tablets.
- ✓ No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling
- ✓ Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- ✓ Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs.
- ✓ Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improved clinical performance through a reduction of unwanted effects.
- ✓ Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- ✓ The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

- ✓ Useful in cases where an rapid onset of action required such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma.
- ✓ An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- ✓ Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

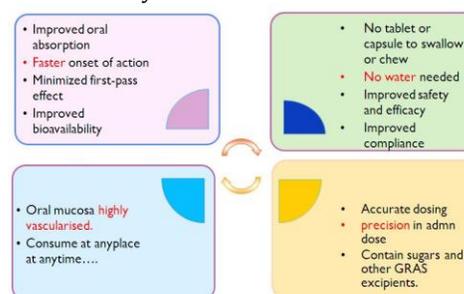


Fig 1: Advantages Of FDF

Disadvantages of FDF²:

- ✓ Drugs which are unstable at buccal pH cannot be administered.
- ✓ Drugs which irritate the mucosa cannot be administered by this route.
- ✓ Drug with small dose requirement can only be administered.
- ✓ Taste masking- Most drugs have bitter taste, and need taste masking.
- ✓ Special packaging- OFDFs are fragile and must be protected from water so it needs special packaging.

Formulation Development:

Sr. No	Category	Con. (%)
1	Drug	1-25
2	Polymer	40-50
4	Plasticizer	25-35
5	Sweetener	2-10
6	Flavor	2-5

Table 1: Formulation of FDF

1. **Choice of drug candidate**
Suitable drug candidate for FDF should possess:
 - ✓ No bitter taste.
 - ✓ Good stability in water and saliva.
 - ✓ Dose should be low as possible.

Various categories of drugs such as antiemetic neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorants, anitussive^{6,7,13-22}.

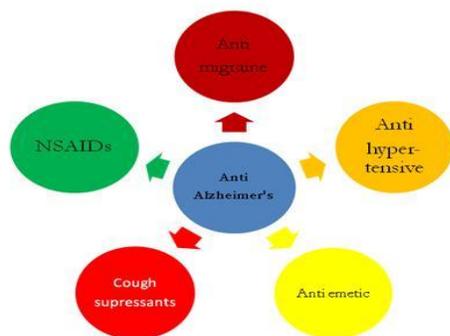


Fig 2: Candidate Drugs.

2. Selection of Polymers ^{2,8,9,11}

For the preparation of FDF the various Polymers can be used in the film upto 40% w/w of the film content. The polymers are responsible for the strength of the film. The film should be tough to prevent damage during handling and transportation. The polymers can be use as single or in combination as per requirement. The Name of the polymers is as follows ¹³⁻¹⁹.

- ✓ Hydroxyl propyl methyl cellulose (HPMC)
- ✓ Hydroxy Propyl cellulose
- ✓ Starch and modified starch
- ✓ Pullunan
- ✓ Pectin
- ✓ Gelatin
- ✓ Carboxy methyl cellulose
- ✓ PVP + Cross linked PVP
- ✓ Alginates
- ✓ Poly vinyl Alcohol
- ✓ Maltodextrose
- ✓ Polyox



Fig3: Preparation of FDF using Different polymers

Among this the Pullulan and HPMC are the best suitable polymers for the preparation of FDF. Pullulan is a neutral glucan (like Amylose, Dextran, Cellulose), with a chemical structure somewhat depending on carbon source, producing microorganism (different strains of Aureobasidium pullulans), fermentation conditions. HPMC is propylene glycol ether of methylcellulose. The low viscosity grades of HPMC are use for the preparation of FDF like HPMC E3/E5/E6/E15.

3. Plasticizer ^{2,10}

The role of Plasticizer is beneficial for preparation of FDF. Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the film. The plasticizer should be compatible with polymer and solvent. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer ^{11,12}.

Propylene glycol (PG), Poly ethylene Glycol (PEG), Glycerol, Phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer. Plasticizer may lead to film cracking, splitting and peeling of the film ². It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug ²³. The Plasticizer should be volatile in nature.

4. Flavorant ²

Flavorants includes:

1. Both natural and artificial flavor such as artificial vanilla, cinnamon, and various fruit flavors; either individual or mixed
2. Mints such as peppermint, menthol.
3. Essential oils such as thymol, eucalyptol and methyl salicylate.

5. Sweeteners ^{2,17}

Sweeteners include both natural and artificial sweeteners as:

1. Natural sweeteners include monosaccharide's, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof;
2. Water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like and free acid form of saccharin and dipeptide based sweeteners.

Aspartame, Neotame are successfully use for the taste masking ^{8,24}.

6. Saliva stimulating agent ^{2,25}

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 FDF. Generally acids which are used as salivary stimulants. Citric acid,

malic acid, lactic acid, ascorbic acid and tartaric acid are the few

examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%^{2,25}.

Methods of Preparation Of FDF 2,20,22:

The following processes can be used to manufacture the oral fast dissolving films.

1) Solvent Casting Method:

- Preparation of the casting solution,
- Deaeration of the solution,
- Transfer of the appropriate volume of solution into a mold,
- Drying the casting solution,
- Cutting the final dosage form to contain the desired amount of drug,
- Packaging.

The oral fast dissolving films are prepared by dissolving strip forming agents, plasticizer and saliva stimulating agent in the distilled water, then solution is continuously stirred up to 4 hr on magnetic stirrer and kept for 1 hour to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining water soluble excipients i.e. sweetening agent, disintegrating agent, saliva stimulating agent, flavor and drug are dissolved with constant stirring for 45 min. When the stirring is over both the solutions are mixed together with stirring for another 1 h on magnetic stirrer. Then keep the solution stationary for 1 hr to let the foams settle down. The resulting formulation is casted on a suitable platform and is dried to form a film. The film is preferably air-dried or dried under oven then the film is carefully removed.

2. Hot-melt Extrusion Method:

- In the extrusion process the API and other ingredients are mixed in dry state, subjected to heating process and then extruded out in molten state.
- In this process, solvents are completely eliminated. The strips are further cooled and cut to the desired size.
- The high temperature used in this process may degrade thermolabile APIs.

Drug and polymers are blended into a sigma blade mixer for 10 min, and then plasticizer is slowly added. The mixture is granulated in the presence of an anti-sticking agent. Granules are stored overnight at room temperature and then sieved through a 250 µm sieve in order to remove the excess of powder and standardize the particle size. The dried granular material is fed into the extruder. The screw speed is set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. The processing temperatures are set at 80° C (zone 1), 115° C (zone 2), 100° C (zone 3) and 65° C (zone 4).

The extrudate (T = 65° C) is then pressed into a cylindrical calendar in order to obtain a film with a thickness of about 200 µm. At the end of the preparation processes, the films are cut according to the size required for testing, individually sealed in airtight packets and stored at 25°C until use^{5,16}.

3. SEMISOLID CASTING

- Water soluble polymers are dissolved in water
- Solution added to solution of acid insoluble polymer (CAP,CAB) which was prepared in NH₄OH,NaOH.
- Plasticizer is added to obtain gel mass.
- The prepared gel mass is cast into films.
- Thickness : 0.015-0.05 inch

4. ROLLING METHOD

- A solution or suspension containing the drug is rolled on a carrier.
- Solvent : water or water and alcohol
- The film is dried on the rollers and cut into desired size

Evaluation Parameters of Oral Fast Dissolving Films^{2,12-18,25}:

1. Weight of films

Oral fast dissolving films can be weighed on analytical balance and average weight can be determined for each film.¹³ It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

2. Film thickness:

The thickness of the film can be measured by micrometer screw gauge (Acculab) at three different places; averages of three values can be calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film^{2,17,18}.

3. pH value:

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH value¹⁸.

4. Folding endurance:

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place, either to break the specimen or to develop visible cracks). This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The folding endurance of the strips can be determined by repeatedly folding one film at the same place till it broke.^{7,19}

5. Content Uniformity

Drug content can be determined by dissolving the film in 100 ml of suitable solution to get 20 µg/ml solutions. An aliquot of 2ml sample can withdraw and diluted to 10 ml with solution. Then solution can be

filtered through whatman filter and solution analyzed spectrophotometrically.

6. In Vitro Dissolution Studies

The in vitro dissolution study can be carried out in 500 ml pH 6.8 phosphate buffer or 0.1N HCl using (USP) XIV paddle apparatus II at $37 \pm 0.5^\circ\text{C}$ and at 50 rpm. Each square cut film sample is submerged into the dissolution media and appropriate aliquots were withdrawn at specific intervals for 30 min. The drug concentration is measured by a UV spectrophotometer.

7. Morphology Study

Morphology of the prepared film can be observed under a motic electron photomicrograph. Motic electron photomicrographs can be recorded at 100 X magnification¹².

8. Stability Studies²⁵

Stability studies on the optimized formulation of oral fast dissolving film is carried out to determine the effect of temperature and humidity on the stability of the drug. The film can be stored in an aluminium foil and subjected to stability at room temperature. The sample can withdraw at 90 days and 180 days and subjected for disintegration test and in vitro dissolution studies to determine disintegration time and cumulative % drug release.

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