



Review Article

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Fast Dissolving Oral films: Easy way of Oral delivery

**Suhas.S Siddheshwar*, Dattaprasad.N.Vikhe, Ganesh.A.Waghmare,
Prashant.B. Wadhule, Prajakta.S. Varpe**

Pravara Rural College of Pharmacy, A/P-Loni, Tal-Rahata, Dist.Ahmednagar, India-413736

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Abstract

Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in gastrointestinal tract and first pass effect can be avoided. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients with fear of choking. Over-the-counter films for pain management and motion sickness are commercialized in the US markets. Many companies are utilizing trans dermal drug delivery technology to develop thin film formats. In the present review, recent advancements regarding fast dissolving buccal film formulation and their evaluation parameters are compiled.

Key words: First pass effect, Lyophilized systems, Nutraceutical, Transdermal, Salivary Stimulants, Oral strips. Tensile strength

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***Corresponding author**

Suhas.S Siddheshwar

Pravara Rural College of Pharmacy,
A/P-Loni, Tal-Rahata, Ahmednagar, India

E-mail: ssiddheshwar@gmail.com

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1. 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 exists despite their short disintegration/dissolution times. The film overcome the danger/fear of choking. 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. Overview of Oral Mucosa

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

Definition of FDF:

Fast dissolving films are most advance form of solid dosage form due to its flexibility. it improve efficacy of Active pharmaceutical ingredient (API) dissolving in short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet

Classification of Fast Dissolving Technology

For ease of description, fast dissolve technologies can be divided in to three broad groups.

- A. Lyophilized systems,
- B. Compressed tablet-based systems,
- C. OTF.

A. Lyophilized systems

This system has been by far the most successful among them in terms of sales value, sales volume, and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste masked materials and have more rapid disintegration than tablet-based systems.

B. Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard high density polyethylene (HDPE) bottles or blisters through to more specialists pack designs for product protection, for example, CIMA Labs, PackSolv. The speed of disintegration for fast dissolving tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or super disintegrate or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is BiovailFuisz Technology. It uses the proprietary Shear form system to produce drug loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies, and generic pharmaceutical companies, for in house development of line extension and generic fast dissolving dosage forms.

C. OTF

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable OTF or OS have evolved over the past few years from confection and oral care markets in the form of breath strips and become a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTF are a proven and accepted technology for systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs gives the comparative account of three different fast dissolving technologies

Classification of OTF

There are three subtypes of oral fast dissolving films:

1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained release wafers.

Special Features of Fast Dissolving Films

- a. Film should be thin and elegant.
- b. Available in various size and shapes.
- c. Unconstructive.
- d. It should adhere to the oral cavity easily.
- e. Should processes fast disintegration without water.
- f. Rapid release.

Advantages of FDF

- a. Convenient dosing.
- b. No water needed.
- c. No risk of choking.
- d. Taste masking.
- e. Enhanced stability.
- f. Improved patient compliance.
- g. Dose accuracy in comparison to syrup.

Disadvantage of FDF

There remain a number of technical limitations with use of film strips; the thickness while casting the film. Glass Petri plates cannot be used for casting.

- a. The other technical challenge with these dosage forms is achieving dose uniformity.
- b. Packaging of films requires special equipments and it is difficult to pack.
- c. Drugs which are unstable at buccal pH cannot be administered.
- d. Drugs which irritate the mucosa cannot be administered by this route.
- e. Drug with small dose requirement can only be administered.
- f. Taste masking- Most drugs have bitter taste, and need taste masking.

Standard Composition of Oral Fast Dissolving Strip

Oral dissolving film is a thin film with an area of 1-20 cm² (depends on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30 mg. Formulation considerations (plasticizers, etc.) have been reported as important factors affecting mechanical properties of the films. lists the standard composition of fast dissolving strip along with the various ingredients used in the formulation of fast dissolving strips.

3. Formulation

1. Drug

The area of drug loaded FDF should be between 1-20cm². The drug can be loaded up to a single dose of 30mg. All excipients used in the fast dissolving film should be generally regarded as safe (GRAS-listed) and authorized for use in oral strip. Formulation considerations have been reported as important factors which affected mechanical properties of the films .

A typical composition contain following

S. No.	Ingredients	Amount (w/w)
1.	Drug	1-30%
2.	Film forming polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva stimulating agent	2-6%
5.	Sweetening agent	3-6%

- | | | |
|----|-----------------|------|
| 6. | Flavoring agent | q.s. |
| 7. | Surfactant | q.s. |
| 8. | Coloring Agent | q.s. |

Active Pharmaceutical Ingredient: A distinctive composition of the film contains 1-30%w/w of the active pharmaceutical ingredient. Always use low dose active pharmaceutical ingredients used because high dose of drug are difficult to incorporate in fast dissolving film micronized API is useful because it enhances the texture of film and provides improved dissolution and uniformity in the fast dissolving film. A number of drugs can be used as fast dissolving oral film.

2. Film Forming Polymers

A variety of polymers are available for preparation of fast dissolving oral films. The use of film forming polymers in oral films has attracted considerable attention in medical and nutraceutical applications. The selection of film forming polymers, is one of the most important and critical parameters for the successful development of film formulation. The polymers can be used alone or in combination to provide desired film properties. The polymers used in oral film formulation should be:

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spreadability property.

3. Plasticizers:

Plasticizer is a very important ingredient of oral strip formulation. It helps to improve the flexibility and reduce the brittleness of the fast dissolving film and by addition of plasticizers, tensile strength and elongation can be improved. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of oral strip.

4. Sweetening Agent:

Sweeteners have become the essential part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Both natural and artificial sweeteners are used in the formulation to improve the palatability of the fast dissolving film. Generally sweeteners are used in the formulation in concentration of 3-6% w/w, either alone or in combination.

5. Saliva Stimulating Agent:

The rationale of employing saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the fast dissolving film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants, like- citric acid, malic acid, lactic acid, ascorbic acid etc. These are used alone or in combination between concentration 2 to 6%w/w of the film. Sweeteners also act & as saliva stimulating agent.

6. Surfactant:

Surfactants are used as solubilizing or wetting or dispersing agents so that the film gets dissolved within seconds and releases the active agent instantly. Several numbers of surfactants are used in oral strips. One of the most important surfactants is polymer 407 that is used as solubilizing, wetting and dispersing agent.

7. Flavoring Agent:

Selection of flavor is depending on which type of drug is to be incorporated in the formulation. The recognition of the oral disintegrating/ dissolving formulation by an individual depends on the initial flavor quality which is observed in the first few seconds after the product has been consumed and the after taste of formulation lasts for at least 10 min. The amount of flavor required to mask the taste depends on the flavor type and its strength. Flavoring agent is used in the formulation in concentration of 10% w/w.

4. Method of Preparation

One or more of the following processes can be used to combine to manufacture the mouth dissolving films.

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

Solvent casting method

- In solvent casting method excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution.
- Finally solution is casted in to the Petri plate and dried.

- Polymer dissolved in solvent + Drug & excipient dissolved in suitable.
- To form solution solvent. Both solution are mixed with rapid stirring.
- Homogenous solution is then spread on flat surface dried and film formed

Advantage:

- Great uniformity of thickness & great clarity than extrusion.
- Films have fine gloss & freedom from defect such a die lines.
- Films have more flexibility & better physical properties.

Disadvantage:

- The polymer must be soluble in a volatile solvent or water.
- The stable solution with reasonable minimum solid content & viscosity should be formed.

Semisolid Casting Method:

- Solution of water soluble film forming polymer is prepared
- Resulting solution is added to a solution of acid insoluble polymer (E.g. cellulose acetate phthalate, cellulose acetate butyrate)
- Appropriate amount of plasticizer is added to obtained gel mass
- Gel mass is casted into the films or ribbons using heat controlled drums
- 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

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
- Incorporated solution into the melt of polyethylene glycol, below 70°C II
- Solid dispersions are shaped into the films by means of dies

Hot Melt Extrusion:

- a. The drug is mixed with carriers in solid form
- b. Extruder having heaters melts the mixture
- c. Finally the melted mixture is shaped in films by the dies

Advantages:

- a. Fewer operation units
- b. Better content uniformity
- c. An anhydrous process

Rolling Method:

A 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 gives desired shape and size

Evaluation Parameters

- a. Thickness
- b. Dryness/tack test
- c. Tensile strength
- d. Percent elongation
- e. Tear resistance
- f. Young's modulus
- g. Folding endurance
- h. In vitro disintegration test
- i. Drug content uniformity
- j. Surface pH test
- k. Contact angle
- l. Transparency
- m. Permeation studies
- n. Stability study

Thickness

The thickness of film is measured by micrometer screw gauge or calibrated digital Vernier Calipers. The thickness of film should be in range 5-200 μm . The thickness should be evaluated at five different locations (four corners and one at centre) and it is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film.

Dryness/tack test

In all there have been eight stages identified for film drying and these are set-to-touch, dust-free, tack-free (surface dry), dry-to touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat, and dry print-free. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with strip. Instruments are also available for this study.

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of strip.

Percent elongation

When stress is applied on a film (2×2 cm²) sample it gets stretched, this is referred to strain. Strain is basically the deformation of strip before it gets broken due to stress. It is measured by using Hounsfield universal testing machine. Generally elongation of strip increases as the plasticizer content increases.

Tear resistance

Tear resistance is the resistance which a film offers when some load or force is applied on the film specimen. The load mainly applied is of very low rate 51 mm/min. The unit of tear resistance is Newton or pounds-force. In other words it is the maximum force required to tear the specimen.

Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Folding endurance

Folding endurance gives the brittleness of a film. The method followed to determine endurance value is that the film specimen (2×2 cm²) is repeatedly folded at the same place until it breaks or a visible crack is observed. The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value.

In vitro disintegration test

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30 s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time. In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to break or disintegrates.

Surface pH test

The surface pH of fast dissolving strip can cause side effects to the oral mucosa, so it is necessary to evaluate the surface pH of film. The surface pH of film should be 7 or close to neutral. For this purpose, a combined pH electrode can be used. With the help of water, OS was made slightly wet and the pH was measured by bringing electrode in contact with surface of oral film. This study should be done on at least six films of each formulation and their mean \pm SD can be calculated. In another method to determine the surface pH, the films are placed on the 1.5% w/v agar gel and then the pH paper are placed on the film, change in color of pH paper gives surface pH of the film.

Contact angle

Contact angle measurement predicts the wetting behavior, disintegration time, and dissolution of oral film. These measurements are performed with help of goniometer (AB Lorentzen and Wettre, Germany) and the measurements should be done at room temperature. The water used to determine contact angle should be double distilled water. A drop of double distilled water is placed on the surface of dry film. Images of water droplet are recorded within 10 s of deposition by means of digital camera. Digital pictures can be analyzed by imageJ 1.28v software (NIH, USA) for angle determination.

Drug content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%.

Transparency

To determine transparency of oral film, a simple ultraviolet (UV) spectrophotometer can be used. The film specimen is placed on the internal side of spectrophotometer cell.

Percentage moisture loss

To determine percentage moisture loss films of area 2×2 cm² are cut and weighed accurately on an electronic balance. After weighing, the films were kept in desiccators containing fused anhydrous calcium chloride. The films should be kept for 72 h in the desiccator. After 72 h, they are taken out and again weighed and the percentage moisture loss of films was measured by using the formula:

Percent moisture loss = $(\text{Initial weight} - \text{Final weight}) \times 100$

Initial weight: The percentage moisture loss studies are done to determine physical stability and integrity of the film.

Stability study

Stability study should be carried out according to the International Conference on Harmonization (ICH) guidelines. The prepared formulation was wrapped in a special way. Firstly, it was wrapped in a butter paper then above it an aluminum foil was wrapped and the packing should be placed in an aluminum pouch and make it heat sealed. The storage conditions at which formulations are kept should be 30°C/60% relative humidity (RH) and 40°C/75% RH. After 3 months, the films were evaluated for drug content, disintegration time, and physical appearance observation..

Storage and packaging of OS

Fast dissolving strips can be packed using single pouches, blister card with multiple units, multiple-unit dispenser, and continuous roll dispenser. There are certain patented packaging systems for fast dissolving films such as Rapidcard by Labtec and Core-peel by Amcor flexible. The rapid card is of same size as a credit card and holds three films on each side. Every dose can be taken out individually.

Applications of OTF in Drug Delivery Systems

- a. Oral mucosal delivery via sublingual, buccal, and mucosal routes by use of oral thin film could become preferential delivery method for therapies requiring rapid drug absorption, including those used to manage pain, allergies, sleep, and central nervous system disorders.
- b. Topical applications: The use of dissolvable films may be feasible in delivery of active agents such as analgesic or antimicrobial agents in the wound care and other applications.
- c. Gastro retentive delivery system: Dissolvable films are being considered in the dosage form for which water soluble and poorly soluble molecules of various molecular weight are contained in film format. Dissolution of film could be triggered by pH or enzyme secretion of gastrointestinal tract (GIT) and could potentially be used for treatment of gastrointestinal disorder.
- d. Diagnostic devices: Dissolvable films may be loaded with sensitive reagent to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device

5. Conclusion

Fast dissolving films are the novel approach in oral drug delivery systems. It promises patient compliance especially in case of pediatrics and geriatrics patients. They can also be used when quick action is required. They possess many advantages over conventional dosage form and can also be used in cases of dysphagia, Parkinson's disease, mucositis, or vomiting.

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