

**Orodispersible Film: A Novel Approach for Patient Compliance****Rajesh Asija^{*}, Manmohan Sharma, Avinash Gupta, Shailendra Bhatt**

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*E-mail: asijar@gmail.comAvailable online **5 October 2013****Abstract**

Orodispersible films are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or chewing. More recently, Orodispersible films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patient's fear of choking. Oral dissolving films are formulated by incorporating the drug with selected oral cavity absorption enhancers in a specially designed oral dissolving film carriers. The oral film technology is still in the beginning stages and has bright future ahead because it fulfill all the need of patient. Mouth dissolving films (MDFs) are another FDDDS evolved over the past few years from the confection and oral care markets in the form of breath strips and became 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 MDFs formats. Today, FDDDS are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications.

Key words: Orodispersible film, FDDDS, Mouth dissolving film, API**Introduction**

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. More than 70% of drug are available in market in the form of oral drug delivery system due to pain avoidance and versatility (to accommodate various types of drug candidates)^{1,2}. As a site of drug delivery, oral cavity offers advantage over the conventional gastrointestinal route and the parenteral and other mucosal route of drug administration. It provides direct entry into the systemic circulation thereby avoiding the hepatic first pass effect, ease of administration. Intraoral drug delivery has become an important route of drug administration. Various intraoral dosage forms have been developed, which includes tablets, capsule, gel, ointment, patches and fast dissolving drug delivery system (FDDDS). FDDDS is most convenient mode of administering drugs to overcome problem related to swallowing difficulties. These delivery systems dissolve or disintegrate in mouth rapidly, without requiring any water to aid in swallowing^{3,4}.

FDDDS was introduced in late 1970 as the alternative to conventional tablet, capsule and syrups especially for the geriatric and paediatric patients suffering from the dysphasia problem. The first developed fast-dissolving dosage form consisted in tablet form, and the rapid disintegrating properties were obtained through a special process or formulation modifications. More recently, Mouth- dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of choking and overcome patent impediments^{5,6}.

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 swallowed⁷.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at \$500million in 2007 and could reach \$2 billion. More importantly, prescriptions of fast dissolving films have been now approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly^{8,9}.

The United States provides the greatest market opportunity for fast dissolve dosage forms followed by Europe and Japan as shown in fig.1¹⁰.

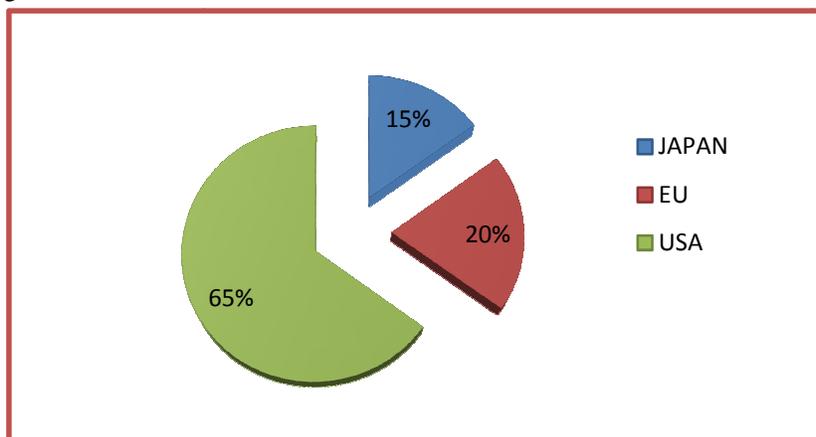


Fig. 1: Fast-dissolve market share by region

Advantages^{1,2}:

1. Oral cavity has large surface area which leads to rapid dissolution and disintegration of the oral dosage form.
2. No risk of choking
3. Mouth dissolving films are solid unit dosage form so provide accurate dosing and great precision.
4. Due to pregastric absorption the bioavailability of drug is improved and fewer doses are required which improve the patient compliance.
5. MDF's does not require water to swallow so it has better acceptability among the dysphasic patients.
6. Provide good mouth feel.
7. Oral films are flexible and less fragile as compared to MDF's so it can easily transport handled and stored.
8. It avoid first pass metabolism as it directly absorb from the buccal mucosa and enter into the systemic circulation, side effects and dose are reduced.
9. Mouth dissolving films disintegrate immediately within seconds when placed on tongue without the need of water and release one or more API.
10. Stability of the dosage form is enhanced.

Disadvantages¹¹

1. Dose uniformity is a technical challenge
2. Hygroscopic in nature
3. High doses cannot be incorporated
4. Require special packaging for products stability and safety.

Special Features of Mouth Dissolving Films¹²

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release
- Have an acceptable taste
- Give a pleasing mouth feel
- Should not leave residue in mouth.

Ideal Characteristics of a Suitable Drug Candidate¹³

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose upto 40 mg.

- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Comparison between orally fast dissolving films and oral Disintegrating tablets are given in table¹⁴

Orally Dissolving Films	Oral Disintegrating Tablets
It is a film	It is a tablet
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area
Better durable than oral disintegrating tablets	Less durable as compared with oral films
More patient compliance	Less patient compliance than films
Low dose can only be Incorporated	High dose can be Incorporated
No risk of choking	It has a fear of choking

Composition of Formulation^{1, 15, 16}

Mouth dissolving film is a thin film with an area of 5-20 cm² containing an active ingredient. The immediate dissolution, in water or saliva is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 30mg. Formulation considerations have been reported as important factors affecting mechanical properties of the films. The excipients used in formulation of fast dissolving films are also discussed in detail.

A typical composition contains the following:

Active pharmaceutical ingredient	05% to30%w/w
Water soluble polymer	45% w/w
Plasticizers	0-20% w/w
Surfactants	q.s.
Sweetening agent	3 to 6 % w/w
Saliva stimulating agent	2 to 6% w/w
Fillers, colors, flavors etc	q.s.

Active Pharmaceutical Ingredients^{2, 17}

The API used in formulation of the film is in the percentage of the 1-25% with small dose. The micronized API is best suitable candidate for the formulation of the thin film which improves dissolution rate and uniformity in the film. Poorly water insoluble drugs the film is prepared by increasing solubility by complexation with various cyclodextrin. The poloxamer 407 is surfactant used to increase solubility with this complex. Following are some drug candidates which are used in mouth dissolving film formulation.

Molecule	Therapeutic Category	Dose
Chlorpheniramine maleate	Anti-allergic	4.0 mg
Zolmitriptan	Anti-migraine	2.5 mg
Cetirizine	Anti-histaminic	5.0-10.0 mg
Famotidine	Antacid	10.0 mg
Loperamide	Anti-diarrheal	2.0 mg
Ketoprofen	Analgesic	12.5 mg
Dicyclomine	Muscle relaxant	25.0 mg
Nicotine	Smoking cessation	1.0-15.0 mg
Omeprazole	Proton pump inhibitor	10.0-20.0 mg

Water Soluble Polymer¹⁸:

Film forming agents are water soluble polymers which are used in formulation of thin film. These are HPMC E5, HPMC E15, HPMC E50, Microcrystalline Cellulose, Polyvinyl alcohol, Gelatin, Eudragit, Maltodextrin, Pullulans.

Plasticizers¹⁹

The plasticizers are used in the formulation of mouth dissolving film to increase the flexibility by reducing the glass transition temperature of the film. Improper use of plasticizers may affect the mechanical properties of the film. The commonly used plasticizers are PEG 400, Glycerol, Propylene Glycol, Acetyl citrate castor oil etc.

Sweetening agents²⁰

Some of the commonly employed sweeteners are dextrose, sucrose, fructose, glucose, isomaltose, polyhydric alcohols (sorbitol, mannitol), etc. Artificial sweeteners like saccharin, cyclamate, aspartame (first generation) and acesulfame K, sucralose, alitame, neotame (second generation) can also be used.

Surfactants²¹

Surfactants are used as wetting or solubilising or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed are poloxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is poloxamer 407.

Saliva stimulating agent²²

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 rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized 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.

Colouring agents²²

Pigments such as Titanium dioxide or FD & C approved colouring agent are incorporated (not exceeding concentration of 1% w/w) in solution.

Manufacturing Methods

To manufacture fast dissolving oral films, following methods are generally employed:

- a. Semisolid casting.
- b. Rolling.
- c. Solvent casting.
- d. Solid dispersion extrusion.
- e. Hot melt extrusion.

a. Semisolid casting²³

In this method at first a solution of watersoluble film forming polymer is prepared. Then the resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate) which was prepared in ammonium or sodium hydroxide. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. A gel mass is obtained on addition of suitable amount of plasticizer. By the means of heat controlled drums, finally the gel mass is casted in to the films or ribbons.

b. Rolling²⁴

Solvents mainly used in this method are water and mixture of water and alcohol. By the means of high shear processor, active agent and other ingredients are dissolved in small portion of aqueous solvent. Water soluble hydrocolloids are dissolved in water to form homogenous viscous solution. Then the resultant solution or suspension containing drug is rolled on a carrier. Finally obtained film is cut in to desired shapes and sizes.

c. Solvent casting²³

In this method water soluble polymers are dissolved in water and the drug along with other ingredients is dissolved in suitable solvent. Then both the solutions are mixed, stirred, finally casted in to the petri plate and dried.

d. Solid dispersion extrusion²⁴

Firstly solid dispersion is prepared by extruding immiscible components with drug and then shaped in to films by the means of dies.

e. Hot melt extrusion²⁵

In hot melt extrusion method at first drug is mixed with carriers in solid form. Then the mixture is molten by the means of extruder having heaters. Lastly the melt is shaped in to films by the dies.

Evaluation

Film thickness²⁶:

A thickness of the film should be calculated by using micrometer screw gauge. Film should be measured at five positions i.e. central and the four corners and the mean thickness are calculated. This test should be performed on six films of each formulation maximum variation in the thickness of the films should be less than 5% and mean \pm S.D calculated.

Dryness test/tack tests²⁷:

About eight stages of film drying process have been identified and they 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. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OS as well. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.

Tensile strength²⁸:

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 the strip as given in the equation below:

Tensile strength = Load at Failure*100/Strip thickness*Strip Width

Percent elongation²⁹:

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

$\% \text{ Elongation} = \text{Increase in length of strip} * 100 / \text{Initial length of strip}$

Tear resistance³⁰:

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm(2 in.)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newtons (or pounds-force).

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:

$\text{Young's modulus} = \text{Slope} * 100 / \text{Strip thickness} * \text{Cross-head speed}$

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Folding endurance³¹:

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Surface pH³²:

The surface pH of the oral dissolving film is calculated in order to investigate the risk of any side effects *invivo*. Since acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to maintain the surface pH as close to neutral as possible. A combined pH electrode is used for this purpose. The oral film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed in six films of each formulation and mean \pm S.D calculated.

Disintegration time testing³³:

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5-30s. A small amount of medium is used, so natural conditions could be simulated. Due to the use of the Small amount of medium the dissolved drug substance could not be measured by spectral analysis.

1. Slide frame method: one drop of distilled water was dropped by a Pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured.

2. Petri dish methods³⁴: 2 ml of distilled water was placed in a Petri dish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely.

Dissolution test³⁵:

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

Stability studies³⁶:

Stability study is conducted at accelerated condition of 65% relative humidity and 35 °C temperature in the humidity chamber for the three months. After 3 months films are evaluated for the drug content, disintegration time and physical appearance.

Assay/drug content and 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 percent.

Conclusion

The popularity of FDDDS has increased tremendously over the last decade. There are many drugs that have been formulated into marketed FDDDS using various technologies. The key to FDT formulations is fast disintegration, dissolution, or melting in the mouth. FDDDS have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Today, FDDDS are more widely available as OTC products for the treatment of allergies, cold, flu, pain, migraine, hypertension and vomiting symptoms. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand.

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