ORALLY FAST DISSOLVING FILMS: INNOVATIONS IN FORMULATION AND TECHNOLOGY

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ABSTRACT
Orally fast dissolving films (OFDFs) have been introduced in the market recently as they provide convenience and ease of use over other dosage forms such as orally disintegrating tablets. This technology 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, so OFDFs are gaining the interest of large number of pharmaceutical industries. Orally fast dissolving film is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. OFDFs are very similar to postage stamp in their shape, size and thickness. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The present review provides an account of various formulation considerations, method of preparation and quality control of the OFDFs.

Keywords: Fast dissolving films, Fast disintegration, Oral strips, Tensile strength.

INTRODUCTION
Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water1-4.

So, fast-dissolving drug-delivery systems came into existence in the late 1970’s as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention5,6.

Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which 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 and intragastric absorption. Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of $500 million in 2007 and could reach $2 billion in 2012. Based on upward global growth trends of the past decade, the fast dissolving dosage market could produce revenues of $13 billion by 20157,8.

Special features of mouth dissolving films

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

The ideal characteristics of a drug to be selected

- 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.

**Advantage of orally fast dissolving films**

- Oral dissolving films can be administered without water, anywhere, any time.
- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
- Suitability for geriatric and pediatric patients, who experience difficulties in swallowing mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.
- Beneficial in cases such as motion sickness, acute pain, suee episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- 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.
- As compared liquid formulations, precision in the administered dose is ensured from each strip of the film.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
- Provide new business opportunity like product differentiation, product promotion, patent extension.

**Disadvantages**

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.

### Table 1: Comparison between orally fast dissolving films and oral disintegrating tablets.

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

### FORMULATION CONSIDERATION

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Sweetening agent
- Saliva stimulating agent
- Flavoring agent
- Coloring agent

**Active pharmaceutical ingredient**

A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in OFDFs. Multivitamins upto 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OFDFs. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste. This is often termed as obscuration technique.

### Table 2: The drugs which have incorporated via orally fast dissolving films are mentioned below

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol</td>
<td>Anti asthmatic</td>
<td>4</td>
</tr>
<tr>
<td>Levocetrizine</td>
<td>Antihistaminic</td>
<td>75</td>
</tr>
<tr>
<td>Chlorohexidine</td>
<td>Antiseptic</td>
<td>12</td>
</tr>
<tr>
<td>Ondensteron</td>
<td>Anti emetic</td>
<td>2.5</td>
</tr>
</tbody>
</table>
The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, 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 excipients. Typically the plasticizers are used in the concentration of 0-20 percent; w/w of dry polymer weight. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug 22.

Sweetening agents

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sacralose have more than 200 and 600 time sweetness. Neotame and allitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Aspartame was used for the preparation of oral strips of valdecoxib. Sucralose and neotame was reported to be used in the suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron respectively 23, 24.

Saliva stimulating agent

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. Eg. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip 25.

Flavoring agents

Preferably up to 10%w/w flavors are added in the OFDF formulations. The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the
after taste of the formulation which lasts for at least about 10 min. The selection of flavor is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.

**Coloring agents**

FD & C approved coloring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. Eg. titanium dioxide.

**METHOD OF PREPARATION**

One or more of the following process can be used combinely 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.

**Semisolid casting**

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. In Semisolid casting method gel mass is casted in to the films or ribbons using heat controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. Acid-insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

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**Figure 1:** Flow chart of solvent casting method for the preparation of fast dissolving films.
Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. 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 in order to obtain a film. There are certain benefits of hot melt extrusion.28, 29

- Fewer operation units
- Better content uniformity
- An anhydrous process

Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. 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.28

**EVALUATION**

- **Mechanical properties**
  - Thickness
  - Dryness/tack test
  - Tensile strength
  - Percent elongation
  - Young’s modulus
  - Tear resistance
  - Folding endurance
- **Organoleptic test**
- **Swelling test**
- **Surface pH test**
- **Contact angle**
- **Transparency**
- **Assay/Content Uniformity**
- **Disintegration test**
- **In-vitro Dissolution test**

**Thickness**

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations.

**Dryness test/tack tests**

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 OFDF. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. 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.30

**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 the strip as given in the equation below:30

\[
\text{Tensile strength} = \frac{\text{Load at breakage}}{\text{Strip thickness } \times \text{ Strip Width}}
\]

**Percent elongation**

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.30

\[
\% \text{ Elongation} = \frac{\text{Increase in length } \times 100}{\text{Original length}}
\]

**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:

\[
\text{Young’s modulus} = \frac{\text{Force at corresponding strain}}{\text{Cross sectional area } \times \text{ Corresponding strain}} \times 1
\]

Hard and brittle strips demonstrate a high tensile strength and Young’s modulus with small elongation.30

**Tear resistance**

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).30

**Folding endurance**

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.31, 32
Organoleptic evaluation

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations.

Surface pH of film

Surface pH of the films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the colour of pH paper was observed and reported31, 32.

Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed31, 32.

The degree of swelling was calculated using parameters
\[
a = \frac{w_t - w_0}{w_0}
\]
where \(w_t\) is weight of film at time \(t\), and \(w_0\) is weight of film at time zero.

Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows:

\[
Transparency = \frac{\log T_{600}}{b} = -c
\]

Where \(T_{600}\) is the transmittance at 600 nm and \(b\) is the film thickness (mm) and \(c\) is concentration33, 34.

Assay/ 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.

Disintegration time

Disintegration of orally fast dissolving films requires USP disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films strips30.

Dissolution test

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 employed30.

Table 3: Commercial Thin Film oral Dosage Form Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Active Pharmaceutical Agent</th>
<th>Strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triaminic</td>
<td>Novartis</td>
<td>Dextromethorphan HBr</td>
<td>7.5</td>
</tr>
<tr>
<td>Triaminic</td>
<td>Novartis</td>
<td>Diphenhydramine HCl</td>
<td>12.5</td>
</tr>
<tr>
<td>Theraflu</td>
<td>Novartis</td>
<td>Dextromethorphan HBr</td>
<td>15</td>
</tr>
<tr>
<td>Gas-X</td>
<td>Novartis</td>
<td>Simethicone</td>
<td>62.5</td>
</tr>
<tr>
<td>Sudafed</td>
<td>Pfizer</td>
<td>Phenylephrine HCl</td>
<td>10</td>
</tr>
<tr>
<td>Benadryl</td>
<td>Pfizer</td>
<td>Diphenhydramine HCl</td>
<td>12.5</td>
</tr>
<tr>
<td>Chloraseptic</td>
<td>Prestige</td>
<td>Benzocaine Menthol</td>
<td>3/3</td>
</tr>
<tr>
<td>Suppress</td>
<td>InnoZen</td>
<td>Menthol</td>
<td>2.5</td>
</tr>
<tr>
<td>Orajel</td>
<td>Del</td>
<td>Menthol/Pectin</td>
<td>2/30</td>
</tr>
<tr>
<td>Listerine</td>
<td>Pfizer</td>
<td>Cool mint</td>
<td>-</td>
</tr>
</tbody>
</table>

CONCLUSION

OFDFs are not well defined in the literature but, no doubt a revolutionary and an innovative drug delivery system for all the population groups, specifically geriatric, pediatric patients and patients with swallowing difficulties. OFDFs are also having great potential of delivering the medicinal agent systemically as well locally and have several advantages over many dosage forms even over the fast disintegrating tablets. This explains the extensive research actively going on this technology.
REFERENCES


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Mr. Bhupinder Bhyan graduated from Kurukshetra University Kurukshetra, Haryana. He is doing post graduation in Pharmaceutics from Lovely Professional University (Punjab), completed master thesis in “Formulation and Evaluation of Fast Dissolving Film of An Antimigraine drug”.