INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients.

However, some patients, particularly pediatric and geriatric patients, 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. Hence orally dissolving tablets have come into existence. The OTFs place as an alternative in the market due to consumer’s preference for a fast-dissolving product over conventional tablets / capsules.

The OTF place as an alternative in the market due to consumer’s preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients.

Oral Thin Film

OTF also known as or dispersible film by the European Medicines Agency have attracted significant research and acceptance recently. The idea of OTFs was first presented in the 1970s to overcome swallowing difficulties that the traditional dosage forms like capsules and tablets exhibited.

Normal oral flora comprises a diverse array of organisms which includes eubacteria, archaea, fungi, mycoplasmas and protozoa. Among these, fungi are classified as eukaryotes, and the most important to dentistry belong to the genus Candida. Human infections caused by Candida albicans and other related species range from the more common oral thrush to fatal, systemic superinfections in patients who are afflicted with other diseases.

Pseudomembranous candidiasis is the most commonly recognized type of candidiasis and is also known as thrush. It is seen more often in immunocompromised individuals, in such conditions patient has difficulty in swallowing hence oral thin film is suitable approach.
Advantages

- Lower doses
- Minimal side effects
- Site specific action and local action
- Availability of larger surface area that leads to rapid disintegration and dissolution in the oral cavity and promote the systemic absorption of APIs
- No need of water or a spoon for administration.
- Rapid onset of action
- Destructive acidic environment of stomach can be avoided Minimal side effects
- Delivery can also be terminated relatively easily if required.

Disadvantages

- The disadvantage of OTF is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight. Novartis Consumer Health’s Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip
- Expensive packaging of oral film

Limitations:

- Drugs with larger doses are difficult to formulate into film e.g. rifampin (600 mg), ethambutol (1000mg) etc. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health’s Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip
- Most bitter drugs should be avoided or taste masking is required.
- Proteinaceous drugs should be avoided if used then co-administration of enzyme inhibitors such as aprotinin, bestatin, puromycin and bile salts required for the inhibition of proteolytic enzymes present in saliva.

Mechanism of action:

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the 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 absorption or with formula modifications, will maintain the quick-dissolving aspects.\(^1\)

Classification of oral films

There are three types of oral films:

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

### Table 1: Types of wafers and their properties\(^2\)

<table>
<thead>
<tr>
<th>Property/Sub Type</th>
<th>Flash release water</th>
<th>Mucoadhesive melt-away wafer</th>
<th>Mucoadhesive sustained release wafer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (cm(^2))</td>
<td>2-8</td>
<td>2-7</td>
<td>2-4</td>
</tr>
<tr>
<td>Thickness(m)</td>
<td>20-70</td>
<td>50-500</td>
<td>50-250</td>
</tr>
<tr>
<td>Structure</td>
<td>Film: single layer</td>
<td>Single or multilayer system</td>
<td>Multi layer system</td>
</tr>
<tr>
<td>Excipients</td>
<td>Soluble, highly hydrophilic polymers</td>
<td>Soluble, hydrophilic Polymers</td>
<td>Low/Non-soluble Polymers</td>
</tr>
<tr>
<td>Drug phase</td>
<td>Solid solution</td>
<td>Solid solution or suspended drug particles</td>
<td>Suspension and/or solid solution Application</td>
</tr>
<tr>
<td>Application</td>
<td>Tongue (upper palate)</td>
<td>Gingival or buccal Region</td>
<td>Gingival, (other region in the oral cavity)</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Maximum 60 seconds</td>
<td>Disintegration in a few minutes, forming gel</td>
<td>Maximum 8-10 hours</td>
</tr>
<tr>
<td>Site of action</td>
<td>Systemic or local</td>
<td>Systemic or local</td>
<td>Systemic or local</td>
</tr>
</tbody>
</table>

\(^1\) Available online at www.journalforpharma.com

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Structure of oral mucosa

Oral mucosa contains following three layers of cells:

i) Stratified squamous epithelium - It’s the outermost layer of the oral cavity. Basement membrane is the interface between connective tissue and epithelium.

ii) Lamina propria - It’s a connective tissue present below basement membrane.

iii) Sub mucous membrane - It is the innermost layer of the oral cavity.

### FORMULATION COMPONENTS FOR ORAL THIN FILM

- Active pharmaceutical ingredients
- Strip forming polymers
- Plasticizers
- Sweetening agents
- Saliva stimulating agents
- Flavoring agents
- Coloring agents
- Surfactants

**Active pharmaceutical ingredients**

The main disadvantage of oral strip/film is the size of the dosage form due to which high dose could not be loaded. We incorporate 5% w/w to 30% w/w of active pharmaceutical ingredients. For multivitamins, up to 10% w/w of dry film weight was loaded. APIs can be milled, micronized or loaded in the form of nanocrystals or particles depending upon the ultimate release profile desired. For bitter drugs taste required to be masked before incorporating APIs in the OS. To enhance the taste, different techniques are used but the simplest method includes mixing and co-processing of bitter testing API with excipient with good pleasant taste called as obscuration technique. Regiospecific delivery of the drugs would also be required in allergy, cough, sore throat and other local oral manifestations.

Table 2: List of drug molecule that can be incorporated in the oral strip.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine maleate</td>
<td>4mg</td>
<td>Anti allergic</td>
</tr>
<tr>
<td>Triplolidine hydrochloride</td>
<td>2.5mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Loperamide</td>
<td>2mg</td>
<td>Anti diarroheal</td>
</tr>
<tr>
<td>Famotidine</td>
<td>10mg</td>
<td>Anti diarroheal, Antacid</td>
</tr>
<tr>
<td>Azatidine maleate</td>
<td>1mg</td>
<td>Anti histaminic</td>
</tr>
</tbody>
</table>

Table 3: List of some film forming polymers

<table>
<thead>
<tr>
<th>Natural Polymers</th>
<th>Synthetic Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>Hydroxy propyl methyl cellulose</td>
</tr>
<tr>
<td>Pectin</td>
<td>Poly vinyl pyreraldine (PVP)</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Polyvinyl alcohol (PVA)</td>
</tr>
<tr>
<td>Sodium alginante</td>
<td>Sodium Carboxy methyl cellulose</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>Poly ethylene oxide (PEO)</td>
</tr>
<tr>
<td>Pullulan</td>
<td>Kollicoat IR</td>
</tr>
<tr>
<td>Xanthan</td>
<td>Hydroxy propyl cellulose (HPC)</td>
</tr>
<tr>
<td>Polymerized rosin</td>
<td>Hydroxy ethyl cellulose (HEC)</td>
</tr>
<tr>
<td>Gum acacia</td>
<td>Methyl cellulose (MC)</td>
</tr>
</tbody>
</table>

**Ideal properties of the film forming polymers**

- The polymer employed should be non-toxic, nonirritant and devoid of any leachable impurities.
- It should be tasteless.
- It should have good wetting and spreading ability.
- The polymer should exhibit sufficient peel, shear and tensile strength.

### Strip forming polymers

Polymer is the major and most essential component of FDOFs. A variety of polymers are available for preparation of oral film and these are used in the concentration of about 40-45% w/w of total film weight but can be increased up to 65% w/w of film weight alone or in a combination to obtain desired properties of oral film. The film obtained should be tough enough so that there may not be any damage while handling or during transportation. The robustness of the film depend on the type of polymer and the amount in the formulation. The physicochemical characteristic of the polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the prepared film.

**Table 3: List of some film forming polymers**

- Sumatriptan succinate: 35-70mg Anti migraine
- Ketoprofen: 12.5mg Analgesic
- Nicotin: 2mg Smoking cessation
- Psuedoephedrine hydrochloride: 30mg Bronchodilator
- Acrivastine: 8mg Anti histaminic
- Dextromethorphan Hydrochloride: 10-20mg Cough suppressant
- Loratadine: 10 mg Anti histaminic
- Diphenhydramine hydrochloride: 25 mg Anti allergic

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• The polymer should be cheap and readily available.
• It should have long shelf life.
• It should not cause any secondary infections in the oral mucosa/dental region.
• It would be ideal to have a polymer that would have local enzyme inhibition action along

• Plasticizers:

Plasticizer is a vital ingredient of the OS formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer.\textsuperscript{10,11} 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. However inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip.\textsuperscript{12-14} It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.\textsuperscript{15} The Plasticizer employed should impart the permanent flexibility to the strip and it depends on the volatile nature plasticizer and the type of interaction with the polymer. It should be noted that the properties of plasticizer are important to decrease the glass transition temperature of polymer in the range of 406°C for non aqueous solvent system and below 75 °C for aqueous systems. Plasticizer should be compatible with drug as well as other excipients used for preparation of strip. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyls. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both Hydro Melllose as well as polyvinyl alcohol films.\textsuperscript{16}

• Sweetening agents

Generally, sweeteners are used to mask the bitter taste of certain drugs. Both natural and artificial sweeteners can be used alone or in combination.

Various natural and artificial sweeteners used in fast dissolving oral thin films

1 Natural sweeteners xyllose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids

2 Artificial sweeteners

First generation- Saccharin, cyclamate and aspartame

Second generation- acesulfame-K, sucralose, alitame, neotame

• Saliva stimulating agents

More saliva production helps in the faster disintegration of the fast dissolving film formulations. So the formulations should contain acids which are used in the preparation of food 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

Flavoring agents

Selection of flavour is depending on which type of drug is to be incorporated in the formulation. The acceptance of the oral disintegrating/ dissolving formulation by an individual depend on the initial flavour 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 flavour required to mask the taste depend on the flavour type and its strength. Flavouring agent is used in the formulation in concentration of 10%w/w.\textsuperscript{17} The flavors enhance the acceptance of the formulation and enhance the elegance properties of the film. Selection of flavor depends on which type of drug to be incorporated in the formulation.

The flavoring agents can be selected from synthetic flavor oil, oleo resins, extracts derived from various parts of the plants like of leaves, flowers and fruits. Any flavour can be added such as essential oil or water soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary. Flavors are such as vanillin, chocolate or fruit essence like apple, raspberry, cherry, pineapple etc. The amount of flavor required to mask the taste depend on the flavor type and its strength.\textsuperscript{18}

Basic taste and their taste masking agents\textsuperscript{19,20}

Salt: Butterscotch, maple, apricot, peach, vanilla, mint.
Bitter: Wild cherry, walnut, chocolate, mint, anise.
Sweet: Vanilla, fruit and berry.
Sour: Citrus flavor, licorice, root beer, raspberry

Coloring agents

FD & C approved coloring agents is incorporated in fast dissolving film. Generally colouring agent is not exceeding concentration a level of 1% w/w in fast dissolving film. Mainly titanium dioxide is used in the formulation.

Surfactants

Surfactant are used as a solubilising or wetting dispersing agent so that the film is getting dissolved within seconds and release active agent immediately.\textsuperscript{21}
GENERAL TECHNIQUE FOR PREPARATION FILM

1. Solvent casting
2. Hot melt extrusion
3. Rolling
4. Solid dispersion extrusion
5. Semisolid casting

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

Advantage
- Greater uniformity of thickness and great clarity than extrusion.
- Films have fine gloss and freedom from defect such as die lines.
- Films have more flexibility and better physical properties.

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

2. 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 800°C (zone 1), 1150°C (zone 2), 1000°C (zone 3) and 650°C (zone 4). The extrudate (T = 650°C) then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion
- Fewer operation units
- Better content uniformity
- An anhydrous process.

3. Rolling:
In this method, a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution and suspension should have specific rheological consideration. The solvent is mainly water and a mixture of water and alcohol. The film is dried on the roller and cut to the desired dimensions. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

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. In this method immiscible components are extruded with drug and solid dispersions are prepared. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70°C. Finally the solid dispersions are shaped in to films by means of dies.

5. Semisolid casting method
In this method solution of water soluble film forming polymer is prepared. And resulting solution is added to a solution of acid insoluble polymer (Examples: cellulose acetate phthalate, cellulose acetate butyrate, etc). Then the appropriate amount of plasticizer is added to obtain a gel mass. This gel mass is then casted into the films or ribbons using heat controlled drums. The thickness of the films should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

EVALUATION

1. Thickness
The thickness of film can be measured by micrometer screw gauge or calibrated vernier calipers at different strategic locations (at least 5 locations). It is necessary to determine the uniformity of thickness as it is directly related to accuracy of dose in the film.

2. Weight of film
Four centimetre square of the film was cut and each film weighed on analytical balance. It is desirable that films should have nearly constant weight.

3. Mechanical Properties
Mechanical properties of film include tensile strength, tear resistance, Young’s modulus and percentage elongation.

a) Tensile strength:
Tensile strength is calculated by applying maximum strength on the film and point at which film breaks is noted. Tensile strength of the film is determined by using tensile testing machine.

It is calculated by

\[ \text{Tensile strength} = \frac{\text{Load failure} \times 100}{\text{Strip thickness} \times \text{Strip width}} \]

b) Young’s Modulus:
It is also known as elastic modulus which is used to measure the stiffness of film.

Young’s Modulus = Slope*100/ Film thickness* crosshead speed
c) Percent Elongation:
When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally, elongation of film increases as the plasticizer content increases.

\[
\text{Percent elongation} = \frac{L}{L_0} \\
L = \text{Increase in length of film} \\
L_0 = \text{Initial length of film}
\]

4. Moisture uptake
The previously weighed films are placed in a desiccator for a specific period of time and relative humidity. After three days the film was taken out and weighed for determination of moisture uptake.

Moisture uptake is calculated by
\[
\text{Moisture uptake} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100
\]

5. Moisture content
Weighed films are placed in a desiccator for 24 hours. The films are weighed until there is no further change in weight. It can be calculated by

Moisture content is calculated by
\[
\text{Moisture content} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100
\]

6. Dry test
There are about eight stages of film drying process. 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. These tests are primarily used to paint films, but most of the studies can be revised to evaluate pharmaceutical oral films. Tack is the firmness with which the film adheres to an adjunct (a piece of paper) that has been pressed into contact with the film.

7. Percent elongation
As the stress is applied on the film, the film stretches and this referred to as strain. Strain is basically the deformation of strip divided by the original dimension of the sample. Generally, elongation of strip increases with increase in the concentration of plasticizer.

\[
\text{Percentage of elongation} = \frac{\text{Increase in length of strip}}{\text{initial length of strip}} \times 100
\]

8. Swelling Property
Each film sample is weighed and placed in a pre-weighed stainless steel wire mesh. Then the mesh containing film sample is submerged into 15ml medium (simulated saliva solution) in a plastic container. Increase in the weight of the film was determined at present time interval until constant weight was observed.23

Degree of swelling = \text{Wt} - \text{Wo} / \text{Wo}
Where, \text{Wt} is weight of film at time t,
\text{Wo} is weight of film at time zero

9. Folding Endurance
Folding endurance is determined by repeatedly folding a small strip of film at the same place till it breaks.26

10. Stability testing
For stability testing the oral wafers were stored under controlled conditions of 25 C / 60 % RH as well as 40 C / 75 % over a period of 12 months according to the ICH guideline.27

During storage the oral wafers should be checked for their morphological properties, mass, thickness and reduction of film thickness, tensile properties, water content and dissolution behavior. Consecutively, pH and content during storage are displayed.16

11. 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 for the fast dissolving oral films. Disintegrating time will vary depending on the formulation but generally the disintegration ranges from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films.17

12. Dissolution test
Dissolution testing can be performed in simulated saliva solution or pH 6.4 phosphate buffer using the standard basket or paddle apparatus described in any of the pharmacopoeia at 37±0.5°C. Samples are withdrawn at regular time intervals and analyzed by UV-Visible spectrophotometer.28

CONCLUSION
From the above review it is concluded that the oral thin film is the most effective alternative in the market as per consumer preference. Pediatric and geriatric patients shows more compliance to OTF as compared to other solid dosage forms like tablets and capsules. OTF gives site specific delivery and can be used for number of oral infections.

It has great importance during various conditions like allergy and asthmatic attacks where immediate action is needed. Oral film bridges the gap between consumer preferences and manufacturer.
REFERENCES


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Conflict of Interest: None declared.

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