Overview “A Novel Approach of Fast Dissolving Films and Their Patients”

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Abstract: Recently, fast-dissolving drug delivery systems have started gaining fame and acceptance as new drug delivery systems, which aim to enhance safety and efficacy of a drug molecule by formulating it into a conventional oral dosage form for administration and to achieve better patient compliance. Some companies introduced more robust forms of fast-dissolving drug delivery the film is placed on the top or the floor of the tongue. When put on the tongue, this film dissolves instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such case is enhancing drug bioavailability, No risk of choking, Provide good mouth feel. Fast dissolving drug delivery system to overcome this problem difficulty in swallowing tablets/capsules etc. This review article overview the advancement in the oral dosage forms, application, formulation consideration, method of preparation, evaluation, marketed product and patented technologies of oral fast disintegrating films.

Key words: Fast Dissolving Film - Low Dose - High Solubility - High Permeability - Patient Compliance

INTRODUCTION

Oral route is the most preferred route of administration for systemic effect. About 60% of all the formulations are solid dosage form. Tablet is the most preferred dosage form due to ease of transportation, manufacturing and more patient compliance [1]. Generally geriatric, pediatric and bedridden patients experience difficulties in swallowing the conventional oral dosage form. To overcome this problem a novel formulation was developed i.e. oral fast dissolving films.

Fast dissolving films (FDF), a type of oral drug delivery system for the oral delivery of the drug, was developed based on the technology of the transdermal patch. This delivery system consists of a thin film, which is simply placed on the patient’s tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption [2, 3]. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the oral environment.

FDF is prepared using hydrophilic polymer that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via buccal mucosa [4].

The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability [5].

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 the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet.

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Special feature[6]:
- Available in various size and shape
- Thin elegant film
- Un-obstructive
- Fast disintegration or dissolution
- Rapid release

Advantage [3-8]:
- No risk of choking
- Convenient dosing or accurate dosing
- No need of water to swallow or chew
- Small size for improved patient compliance
- Rapid onset of action
- Ease of handling and transportation
- Improve bioavailability for certain therapeutic ingredient.
- Enhanced stability
- Taste masking

Disadvantages:
- It is hygroscopic in nature so it must be kept in dry places.
- It also shows the fragile, granule property.
- They require special packaging for the products stability and safety
- High dose cannot be incorporated into the oral film.

Development of Oral Solid Dosage Form: Various stages of development of the oral solid dosage formulation [1].

Overview of Oral Mucosa: 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. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [8].

Comparison Between Fast Dissolving Films (FDF) and Fast Dissolving Tablets [9]

<table>
<thead>
<tr>
<th></th>
<th>Fast Dissolving Film</th>
<th>Fast Dissolving Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large surface area gives greater dissolution.</td>
<td>Less surface area gives less dissolution than FDF.</td>
<td></td>
</tr>
<tr>
<td>Fast dissolving films are flexible and durable.</td>
<td>Fast dissolving tablet are brittle and less durable than FDF.</td>
<td></td>
</tr>
<tr>
<td>Only low dose can be incorporated in formulation</td>
<td>High dose can also be incorporated in formulation</td>
<td></td>
</tr>
<tr>
<td>Fast dissolving films are of thickness 0.015-0.05 inches.</td>
<td>Fast dissolving tablet are of same size of conventional tablet</td>
<td></td>
</tr>
<tr>
<td>Patient compliance is more</td>
<td>Patient compliance is less than FDF</td>
<td></td>
</tr>
</tbody>
</table>

Formulation Consideration: 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 [11].

A typical composition contains the following:

<table>
<thead>
<tr>
<th>S. No.</th>
<th>INGREDIENTS</th>
<th>AMOUNT (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Drug</td>
<td>1-30%</td>
</tr>
<tr>
<td>2.</td>
<td>Film forming polymer</td>
<td>40-50%</td>
</tr>
<tr>
<td>3.</td>
<td>Plasticizer</td>
<td>0-20%</td>
</tr>
<tr>
<td>4.</td>
<td>Saliva stimulating agent</td>
<td>2-6%</td>
</tr>
<tr>
<td>5.</td>
<td>Sweetening agent</td>
<td>3-6%</td>
</tr>
<tr>
<td>6.</td>
<td>Flavoring agent</td>
<td>q.s.</td>
</tr>
<tr>
<td>7.</td>
<td>Surfactant</td>
<td>q.s.</td>
</tr>
<tr>
<td>8.</td>
<td>Colors, Filler</td>
<td>q.s.</td>
</tr>
</tbody>
</table>
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 provide improved dissolution and uniformity in the fast dissolving film. A number of drugs can be used as fast dissolving oral film [1, 2, 12].

Below List of few drug that can be incorporated in fast dissolving film [9, 13]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Therapeutic action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azatidine Maleate</td>
<td>1mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Nicotine</td>
<td>2mg</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Loperamide</td>
<td>2mg</td>
<td>Anti diarrheal</td>
</tr>
<tr>
<td>Ondasetron</td>
<td>2.5mg</td>
<td>Anti emetic</td>
</tr>
<tr>
<td>Triplodine hydrochloride</td>
<td>2.5mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Zolmitritpan</td>
<td>2.5mg</td>
<td>Anti migraine</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>4mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Chlorpheniramine Maleate</td>
<td>4mg</td>
<td>Anti allergic</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>5-10mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>8mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Loratidine</td>
<td>10mg</td>
<td>Anti histaminic</td>
</tr>
<tr>
<td>Ompirazole</td>
<td>10-20mg</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>Famotidine</td>
<td>10mg</td>
<td>Antacid</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>12.5mg</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Dicyclomine hydrochloride</td>
<td>25mg</td>
<td>Muscle relaxant</td>
</tr>
<tr>
<td>Diphenhydramine hydrochloride</td>
<td>25mg</td>
<td>Anti allergic</td>
</tr>
<tr>
<td>Sumatriptan succinate</td>
<td>35-70mg</td>
<td>Anti migraine</td>
</tr>
</tbody>
</table>

Film Forming Polymers: Polymers are the most important ingredient of the oral fast dissolving film. Robustness of the film depends on the amount of polymer added in the oral strip. These polymers are mostly attracted considerable attention by medical and neutraceuticals industry. Generally 45% w/w of polymer is used which is based on total weight of dry film. Mainly hydrophilic polymers are used in the oral strip as they rapidly disintegrate in the oral cavity as they come in contact with saliva [14].

Ideal Property of Film Forming Polymer:
- It should be non-toxic and non-irritant.
- Polymer must be hydrophilic.
- It should have excellent film forming capacity.
- It should have good wetting and spread ability property.
- Polymer should be readily available & should not be very expensive.
- Polymer should have low molecular weight.
- It should have sufficient shelf-life.
- Polymer must be tasteless, colorless.
- It should not cause any secondary infection in oral mucosa.
- It should exhibit adequate peel, shear and tensile strengths.

Currently, both natural & synthetic polymers are used for the preparation of fast dissolving film. Now a day’s various natural & synthetic polymers are available in preparation of fast dissolving film [1, 2, 6]

Polymers used in preparation of fast dissolving film [15]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Natural polymer</th>
<th>Synthetic polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pullulan</td>
<td>Hydroxypropylmethyl cellulose</td>
</tr>
<tr>
<td>2</td>
<td>Starch gelatin</td>
<td>Polyvinyl pyrrolidone</td>
</tr>
<tr>
<td>3</td>
<td>Pectin</td>
<td>Polyvinyl alcohol</td>
</tr>
<tr>
<td>4</td>
<td>Sodium alginate</td>
<td>Carboxy methyl cellulose</td>
</tr>
<tr>
<td>5</td>
<td>Maltodextrin</td>
<td>Polyethylene oxide</td>
</tr>
<tr>
<td>6</td>
<td>Polymerized rosin</td>
<td>Kollicoat</td>
</tr>
<tr>
<td>7</td>
<td>Lycoat NG 73</td>
<td>Hydroxypropyl cellulose</td>
</tr>
<tr>
<td>8</td>
<td>Xanthan</td>
<td>Hydroxyethyl cellulose</td>
</tr>
</tbody>
</table>

Various Properties of Few Films Forming Polymer Are Listed below [2, 11]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Hydroxypropyl methyl cellulose</th>
<th>Gelatin</th>
<th>Pullulan</th>
<th>Kollicoat</th>
<th>Starch and modified starch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>10,000-1,500,000</td>
<td>15,000-250,000</td>
<td>8000-2,000,000</td>
<td>About 45000</td>
<td>50,000-1,60,000</td>
</tr>
<tr>
<td>Solubility</td>
<td>Soluble in cold water, insoluble in chloroform, ethanol.</td>
<td>Soluble in glycerin, acid and alkali -Swell in water.</td>
<td>It is soluble in hot as well as in cold water.</td>
<td>&gt;50% in water</td>
<td>Starch is insoluble in cold water and ethanol. It swells in water by about 5 to 10% at 37°C.</td>
</tr>
<tr>
<td>Film forming ability</td>
<td>It has film forming capacity (2-20% w/w concentration).</td>
<td>Very good film forming ability</td>
<td>It has high adhesion and film forming ability</td>
<td>Its provides good film forming properties</td>
<td>Modified starch have a property to form fast dissolving film</td>
</tr>
<tr>
<td>Melting point</td>
<td>190-200°C</td>
<td>—</td>
<td>107°C</td>
<td>—</td>
<td>250°C</td>
</tr>
<tr>
<td>pH</td>
<td>5-8</td>
<td>3.8-6.0</td>
<td>5-7</td>
<td>6.7</td>
<td>—</td>
</tr>
</tbody>
</table>
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 [1, 16].

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 [2, 17].

Saliva Stimulating Agent: The rationale of employing saliva stimulating agents is to increase the rate of production of saliva that would be 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 [3, 6, 18].

| Type of agent used for preparation of fast dissolving film [2, 11, 22, 23] |
|-----------------------------------------------|-----------------|----------------|-----------------|-------------------|-----------------|
| Plasticators | Sweeting agent | Saliva stimulating agent | Surfactant | flavoring agent | Coloring agent |
| Glycerol | Sorbitol | Citric acid | Polaxamer 407 | Pippermint oil | Titanium dioxide |
| Propylene glycol | Sucrose | Malic acid | Sodium laurylesufate | Cinnamon oil | Menthol |
| Polyethylene glycol 400,200,600 | Cyclamate | Lactic acid | Tweens | |
| Dimethyl, Dicetyl, dibutyle Phthalate | Aspartmate | Ascorbic acid | Spans | |
| Triacetin | Neotame | Tartaric acid | Benzalkonium chloride | Lemon oil | |
| Castor oil | Saccharin | | | Chloroform water | |
| Citrate ether | Mannitol | | | | |
| Try ethyle citrate | Acesulfame–K | | | | |

Methods of Preparation of FDF: There are following methods which can be used for preparation of fast dissolving film such as:

- Solvent casting method
- Semisolid casting method
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method [4, 6, 9].

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.
Polymer dissolved in solvent + Drug & excipient dissolved in suitable solvent

To form solution

Both solution are mixed with rapid stirring

Homogenous solution is then spread on flat surface

Dried

Film formed [9, 24]

**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 [17, 18].

**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 70ºC

Solid dispersions are shaped into the films by means of dies[16, 25]

**Hot Melt Extrusion:**

The drug is mixed with carriers in solid form

Extruder having heaters melts the mixture

Finally the melted mixture is shaped in films by the dies [1, 14, 15].

**Advantages:**

- Fewer operation units
- Better content uniformity
- 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 [2, 10, 25].

**Quality Control Test For Fast Dissolving Film**

**Morphology Study:** The morphological study of oral strip is done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API [26].

**Weight Variations:** Weight variation is measured by individually weighting randomly selected 10 films. The average weight should not differ significantly from the average weight [27].

**Thickness:** The thickness of film is determined by micrometer screw gauge at 5 different points of the film i.e. central and the four corners and means thickness is calculated. For measurement of Uniformity of thickness, 5 film are randomly selected and thickness is measured on location of each formulation Maximum variation in the thickness of the films should be less than 5% and mean±S. Dis calculated [6, 28].
Surface pH: The surface pH of oral strip is calculated in order to examine the risk of any adverse effect in vivo. Since acidic or alkaline pH may cause irritation in the oral mucosa, it is determined to maintain the surface pH as close to neutral as possible. The surface pH of oral strip is determined by combined pH electrode [10, 29].

Dryness Test/Track Tests: About eight stage of film drying process have been identified and they are set-to-touch, dust free, track free, dry to touch, dry hard, dry through, dry-to-recoat and dry print free. The details of evaluation of this parameter can be checked tack is the tenacity with which the film adheres to accessory which contact with the strip [1, 30].

Tensile Strength: Tensile strength of film is determined by applying the maximum stress to a point until the oral film breaks. It is calculated by the applied load at rupture divided by the cross section area of the oral film as given in the equation below [3, 31].

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

Percentage Elongation: Percentage elongation is determined by noting the distance travelled by pointer before breaking of the film on the graph paper. Generally elongation of oral strip increase as the plasticizer content increases [2, 32].

\[
\% \text{ Elongation} = \frac{L \times 100}{L^0}
\]

\( L \) = Increase in the length of film,
\( L^0 \) = Initial length of film

Folding Endurance: Folding endurance is measured by manual repeated folding of film at same place till it broke. The number of time the film is folded without breaking is known as the folding endurance value [1, 33].

Tear Resistance: The maximum force required to tear the film is recorded as the tear resistance value. It is expressed in Newton or (pounds –force) [2, 34, 35].

Transparency: The measurement of the oral film transparency can be determined by using a simple UV spectrophotometer. Cut the film sample into rectangles and placed on the internal side of the spectrophotometer cell. Now determine the transmittance of the film at 600 nm. The transparency of film was calculated as follows [1, 35, 36].

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

where
\( T_{600} \) = Transmittance,
\( b \) = Film thickness
\( C \) = Concentration

Young’s Modulus: Young’s modulus is used to determine the stiffness of oral film. It is represented as the ratio of applied stress over strain in the region of elastic deformation. It is calculated as follows: [2, 4, 36, 38].

\[
\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{Cross head speed}}
\]

Assay/drug Content and Content Uniformity: Assay, drug content and drug content uniformity is determined by any standard assay method which is described for the particular API in any standard pharmacopoeia. Limit of content uniformity is 85-115% [40, 41].

Disintegration Time: The disintegration time limit is of 30 sec or less for orally disintegrating tablets, as described in CDER guideline and can be applied to fast dissolving oral film. No official guideline is available for oral fast dissolving films. Pharmacopeial disintegrating test apparatus may be used for this study. Typical disintegration time for film is 5-30 sec [42, 43, 44].

In-vitro Dissolution Test: In-vitro Dissolution study can be performed using the paddle or basket apparatus as described in the pharmacopoeia. The volume of dissolution medium will essentially be selected as per as the sink condition and highest dose of the API. Mainly paddle type dissolution apparatus is used for the dissolution test of oral strip because sometimes the dissolution test can be difficult due to the tendency of the strip to float onto the dissolution medium [45, 46, 47].

Stability Testing: Stability measurement is done by storing the oral strip were stored under controlled conditions of 25°C/60%RH as well as 40°C/75% over a period of 12 months in stability chamber according to the ICH guideline [48, 49].

During storage period various evaluating parameter like thickness, morphological properties, tensile strength, water content and dissolution behavior are checked [50, 51, 52].
Patented Product of Fast Dissolving Film [10] List of some marketed products available as mouth dissolving film

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer/Distributor</th>
<th>API</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listerine</td>
<td>Pfizer</td>
<td>Cool mint</td>
<td>Mouth fresheners</td>
</tr>
<tr>
<td>Triaminic</td>
<td>Novartis</td>
<td>Dextromethorphan HBr</td>
<td>Cough suppressants</td>
</tr>
<tr>
<td>Suppress®</td>
<td>InnoZen®, Inc</td>
<td>Menthol</td>
<td>Anti Flatulating</td>
</tr>
<tr>
<td>Chloraseptic</td>
<td>Prestige</td>
<td>Benzoicaine Menthol</td>
<td>Anti Flattening</td>
</tr>
<tr>
<td>Gas-X</td>
<td>Novartis</td>
<td>Sinemeticon</td>
<td>Anti Flattening</td>
</tr>
<tr>
<td>Theraflu</td>
<td>Novartis</td>
<td>Dextromethorphan HBr</td>
<td>Anti allergic</td>
</tr>
<tr>
<td>Ondansetron ODF</td>
<td>Setofilm</td>
<td>BioalliancePharma</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Ondansetron ODF</td>
<td>Zuplenz(R)</td>
<td>Monosol Rx</td>
<td>Anticancer</td>
</tr>
<tr>
<td>Donepezil film</td>
<td>Donepezil Rapidfilm</td>
<td>Labtec</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>Sudafed PE</td>
<td>Wolters Kluwer Health Inc.</td>
<td>Phenyleprine</td>
<td>Relieving Congestion</td>
</tr>
<tr>
<td>Klonopin Wafer</td>
<td>Solvay Pharmaceuticals</td>
<td>Clonazepam</td>
<td>Treatment of anxiety</td>
</tr>
</tbody>
</table>

Impact in industry: Rotavirus vaccine is prepared in United States by Johns Hopkins University in 2006. Rotavirus vaccine is a room temperature stable quick-dissolving oral thin film delivery system for vaccines that will make vaccinations almost as simple as freshening your breath. This delivery system exhibits many advantages not available in current products. The first of this kind of oral strips were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening [2, 6].

Fast dissolving products has grown rapidly from sales in 2007 of about $850 million & $2billion in near future according to technology catalysts [11, 51, 52, 53].

CONCLUSION

Fast dissolving films have gained popularity because of better patient compliance, rapid onset of action, the drug is directly absorbed into systemic circulation. Oral films have several advantages over the conventional dosage forms. So they are of great importance during the emergency condition like: allergy, Short term spasm and asthma a whenever immediate onset of action is desired.

REFERENCES