FAST DISSOLVING FILMS: INNOVATIVE DRUG DELIVERY SYSTEM


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ABSTRACT

Oral dissolving films are formulated by incorporating the drug with selected oral cavity absorption enhancers in a specially designed oral dissolving film carriers. This facilitates the rapid absorption in the oral cavity for drugs with low GIT-bioavailability and intensive first-pass effects. This it offers shortening onset time, enhancing bioavailability and reducing the probability of first pass side effect.

The current review focuses on the recent development in the oral dissolving film and discusses about its technique for preparation of film as well its evaluation.

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INTRODUCTION:

Some patients have difficulties in swallowing or chewing solid dosage which forms risk or fear of choking so this is a major problem in the use of tablets. Oral dissolving film is a new drug delivery system for oral delivery of drug. The oral route of drug administration is the most important method of administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient’s incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose. Mouth dissolve products (tablets and films) may show greater patient acceptability and convenience. Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing\(^1-2\). After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, Fast-dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. FDFs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething\(^3-5\). Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolve/disintegrate in the mouth within few seconds without water and eliminates the fear of choking as an alternative to fast dissolving tablets. Basically the fast dissolving film can be considered as an ultra thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. Most fast dissolving films are having taste masked active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipients.
The advantages of convenience of dosing and portability of mouth dissolving film have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally. Because of fast dissolving behavior and fast adherence to the mucosa, fast dissolving films cannot be spit after application on to the tongue. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs.

Formulation of fast dissolving film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents. From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms. Fast dissolving films evolved over the past few years from the confection and oral care market in the form by consumers for delivering vitamins and personal care products.

**Special features of Fast Dissolving films**\(^{[6-7]}\):

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

**Advantages**\(^{[8-9]}\):

- Convenient dosing
- No water needed
- Taste masking
- No risk of choking
- Enhanced stability
• Improved patient compliance
• Rapid disintegrating and dissolution in the oral cavity
• Flexible and portable nature provides ease in transportation, handling, storage
• Avoids first past metabolism

Disadvantages\textsuperscript{[10]}:
• High doses cannot be incorporated
• Dose uniformity is a technical challenge
• Hygroscopic in nature
• Require special packaging for products stability and safety

The ideal characteristics of a drug to be selected:
• The drug should have pleasant taste.
• The drug to be incorporated should have low dose less than 30mg.
• 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.

COMPOSITION OF THE SYSTEM:
Mouth dissolving film is a thin film with an area of 5-20 cm\(^2\) containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 15mg. formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films, such as shifting shifting the glass transition temperature to lower temperature\textsuperscript{[11]}.

A typical composition contains the following
Drug 1-25%
Water soluble polymer 40-50%
Plasticizers 0-20%

Fillers, colours, flavours etc. 0-40%

1) **Drugs**

Several classes of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthematics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID’S (e.g. paracetamol, meloxicam, valdecoxib) [12-15].

2) **Water soluble polymers**

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxymethylcellulose 30, Polyvinylpyrrolidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGITRD10[14,15,16,17,18]. Polymerized rosin is a novel film forming polymer [19].

3) **Plasticizers**

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, di-butylphallate, and polyethylene glycols etc [16].

4) **Surfactants**

Surfactants are used as solublising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer407 that is used as solubilizing, wetting and dispersing Agent [20].

5) **Flavour**
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 the formulation which lasts for at least about 10 min. The amount of flavor required to mask the taste depends on the flavor type and its strength. Preferably up to 10% w/w flavors' are added in the formations.\textsuperscript{[21]}

6) Colour

FD&D approved coloring agent are used in the manufacturing of oral dissolving film. (Not exceeding concentration levels of 1% w/w). For example: titanium dioxide.\textsuperscript{[21]}

7) Saliva stimulating agent

Some saliva stimulating agents may also be added to enhance the disintegration and to get rapid release. Some of these agents are citric acid, tartaric acid, malic acid, ascorbic acid and succinic acid.\textsuperscript{[22]}

METHOD OF PREPARATION OF FAST DISSOLVING FILM:\textsuperscript{[23-25]}

One or a combination of the following processes can be used to manufacture the Mouth dissolving film:

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

1. Solvent casting method

Fast dissolving films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

Water soluble ingredients are dissolved in water and
API and other agents are dissolved in suitable solvent to form a clear viscous solution

\[ \text{↓} \]

Both the solutions are mixed

\[ \text{↓} \]

Degassed under vacuum

\[ \text{↓} \]

Resulting solution is cast as a film

\[ \text{↓} \]

Film is dried in drying oven and collected

2. **Hot melt extrusion**:

Hot melt extrusion method has various benefits; those are fewer operation units, minimum product wastage, better content uniformity, an anhydrous process, absence of organic solvents.

In hot melt extrusion method-

Drug is mixed with carriers in solid form.

\[ \text{↓} \]

The extruder having heaters melts the mixture

\[ \text{↓} \]

Finally the melt is shaped in films by the dies.

3. **Semisolid casting method**:

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. 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.

Solution of water soluble film forming polymer is prepared

\[ \text{↓} \]

Resulting solution is added to a solution of acid insoluble polymer

\[ \text{↓} \]
Appropriate amount of plasticizer is added so that gels mass is obtained

↓

Finally the gel mass is casted in to the films or ribbons using heat controlled drums.

4. Solid dispersion extrusion method:

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

↓

Then solution is incorporated into melt of polyethylene glycol, obtainable below 70°C

↓

Finally the solid dispersions are shaped into the films by means of dies.

Precautions while preparing solid dispersions: the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol and polymeric form of drug precipitated in the solid dispersions may get affected by the liquid solvent used.

5. Rolling method:

In this method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film.

Prepare pre-mix with film forming polymer, polar solvent and other additives except a drug

↓

Add pre mix to master batch feed tank

↓

Fed it via a 1st metering pump and control valve to either or both of the 1st and 2nd mixer

↓

Add required amount of drug to the desired mixer

↓

Blend the drug with master batch pre mix to give a uniform matrix
Then a specific amount of uniform matrix is then fed to the pan through 2nd metering pumps.

The film is finally formed on the substrate and carried away via the support roller.

The wet film is then dried using controlled bottom drying.

PATENTED TECHNOLOGIES [26]:

1) SOLULEAVES™:

Soluleaves technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

2) WAFERTAB™:

Wafertab is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The WAFERTAB™ filmstrip can be flavoured for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release, or for use by patients who have difficulty swallowing.
3) **FOAMBURST™**: 

Foamburst is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.

4) **XGEL™**:

Film is at the heart of MeldexInternational's intellectual property, used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is non-animal-derived, approved on religious grounds and is suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing platform. XGEL™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use.

**PACKAGING**:

A variety of packaging options are available for fast dissolving films. In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used. Applied Pharma Research (Switzerland)-Labtec GmbH of Germany has developed the Rapid Card, a proprietary and patented packaging system which is specifically designed for the mouth dissolving films. The Rapid Card is exactly the same size as a credit card and holds three mouth dissolving films on each side. Every dose can be taken out individually, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet and have it readily available[27].

The material selected must have the following characteristics:

- They must protect the preparation from environment conditions.
• They must be FDA approved.
• They must be non-toxic.
• They must protect the preparation from environment conditions.
• They must be FDA approved.
• They must be non-toxic.

**Foil, paper or plastic pouches:** The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

**Single pouch and aluminum pouch:** Soluble film drug delivery pouch is a peel able pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

**Blister card with multiple units** can be used. It consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture[28].

**Barrier films** are used where drug preparations are extremely sensitive to moisture. Several materials may be used to provide moisture protection such as polychlorotrifluoroethylene (PCTFE) film, polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapor barrier. Lack of clarity is still a drawback.

**EVALUATION:**

• Mechanical properties
- Thickness
- Dryness/tack test
- Tensile strength
- Young’s modulus
- Tear resistance
- Folding endurance

- Organoleptic test
- Surface pH test
- Swelling test
- Transparency
- Assay/content uniformity
- Disintegration test
- In-vitro dissolution test

**Thickness**

The thickness of film is determined by screw gauge or micrometer at different points of the films. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

**Dryness/Tack test**

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 orally fast dissolving film. 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 available for this study[29].

**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.

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

**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.

\[
\% \text{ E}l\text{ongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}
\]

**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.

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

**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 51mm (2 in)/min is employed and is designed to measure the force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton’s (or pounds-force).

**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.

**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 methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations.
Morphology Studies:

Scanning electron microscopy (SEM) study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API.

Near-infrared chemical imaging (NIR-CI) study helps in determining the difference between drug distributions in drug loaded films and recrystallization\cite{37}.

Surface pH of film :

Surface pH of films is 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 color of pH paper was observed and reported.

Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a pre-weighed 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 observed\cite{38}.

The degree of swelling was calculated using parameters

\[ S.I = W_t - W_0/W_0 \]

Where S.I is the swelling index, Wt is the weight of the film at time”t”, and Wo is the weight of film at \( t = 0 \).

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 determination transmittance of films at 600 nm. The transparency of the films was calculated as follows:

\[ \text{Transparency} = (\log T_{600})/b = -\epsilon c \]

Where \( T_{600} \) is transmittance at 600 nm and \( b \) the film thickness (mm) and \( c \) is concentration\cite{39-40}.

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**

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 [41].

**Dissolution test**

Dissolution testing can be performed using the standard basket or paddle apparatus. 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 [42]. The list of some of the marketed products is shown in Table No. 1.

<table>
<thead>
<tr>
<th>NO.</th>
<th>Drug</th>
<th>API</th>
<th>Manufacturer / Distributers</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Listerine</td>
<td>Cool Mint</td>
<td>Pfizer</td>
<td>Mouth freshener</td>
</tr>
<tr>
<td>2</td>
<td>Benadryl</td>
<td>DiphenhydramineHCl (12.5mg or 25mg)</td>
<td>Pfizer</td>
<td>Anti allergic</td>
</tr>
<tr>
<td>3</td>
<td>Supress</td>
<td>Methanol (2.5 mg)</td>
<td>InnozenInc</td>
<td>Cough suppressant</td>
</tr>
<tr>
<td>4</td>
<td>Klonopin Wafers</td>
<td>Clonazepam (0.12 mg,0.25mg, 0.50 mg)</td>
<td>Solvay pharmaceutical</td>
<td>Treatment of anxiety</td>
</tr>
<tr>
<td>5</td>
<td>Theraflu</td>
<td>Dextromethorphan HBr (15mg)</td>
<td>Novartis</td>
<td>Anti allergic</td>
</tr>
<tr>
<td>6</td>
<td>Orajel</td>
<td>Menthol / Pectin (2 mg / 30 mg)</td>
<td>Del</td>
<td>Mouth ulcer</td>
</tr>
<tr>
<td>7</td>
<td>GasX</td>
<td>Semethicone (62.5 mg)</td>
<td>Novartis</td>
<td>Antiflatuating</td>
</tr>
</tbody>
</table>
CONCLUSION:

Recently FDF has gained popularity as dosage form and is most acceptable and accurate oral dosage form which bypass the hepatic system and show more therapeutic response. The pharmaceutical companies prefer this dosage form due to both patient compliance (especially pediatric and geriatric) as well as industrial acceptability. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Oral films can replace the over-the-counter (OTC) drugs, generic and name brand from market due to lower cost and consumer’s preference.

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