FAST DISSOLVING ORAL FILMS FOR IMMEDIATE DRUG
RELEASE: A REVIEW

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ABSTRACT

Fast dissolving oral films are the most advanced form of oral solid dosage forms due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity with saliva without chewing and water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin. Fast dissolving oral films are useful for all types of health conditions. The FDOFs plays as an alternative over conventional tablets or capsules. Fast dissolving film combines all the advantages of tablets with those of liquid dosage forms. It has reduced hepatic first pass effect, minimal side effects, dose accuracy and site specific action. The disadvantage of OTF is that high dose of drug cannot be incorporated into strip. FDOFs can be prepared using drug 5-20% w/w, water soluble polymer 45%w/w, plasticizers 0-20%, sweetening agents 3-6%, saliva stimulating agents 2-6%, surfactants, fillers, colours and flavours. The manufacturing methods for oral films are solvent casting, semisolid casting, hot melt extrusion, solid dispersion extrusion and rolling. The oral films can be evaluated by using tack test, tensile strength, tear resistance, swelling index, contact angle measurement, disintegration time and dissolution test. The fast dissolving oral films are most acceptable and accurate oral dosage form which bypass the hepatic system and show more therapeutic response. Oral films can replace the over the counter drugs (OTC).

Keywords: Fast dissolving oral films, Solvent casting, OTF, Extrusion.

INTRODUCTION

Oral route is the most preferred route for the delivery of the drugs than other routes. But oral
drug delivery systems still need some advancements because of their some drawbacks related to particular 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 have difficulty to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its appearance. One study showed that about 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, appearance and taste. The problem of swallowing tablets was more difficult to 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. 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 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 rapid drug releasing products, oral strip technology is gaining much attention5,6.

Orally fast-dissolving film is new drug delivery system for the oral drug delivery and 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 tongue or any oral mucosal tissue, due to saliva it instantly wet, rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal 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.

**Current technologies of Oral Fast-Dispersing Dosage Form**

Out of several technologies, few have reached commercial marketed products. Several methods are available in the preparation of oral fast-dispersing tablets, such as modified tableting systems, floss, or Shearform™ formation by application of centrifugal force, controlled temperature and freeze drying14,15.
Classification Of Fast Dissolve Technology

Fast-dissolve technologies can be divided into three broad groups:

1. Lyophilized systems,
2. Compressed tablet-based systems,
3. Thin film strips.

1. Lyophilized systems

The technology involves taking a suspension or solution of drug with other structural excipients and through the use of a mould forms tablet-shaped units. The tablets are then frozen and lyophilized in the mould. The resulting tablets have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration\textsuperscript{44}.

Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs. The dose capability being slightly lower for some tablet based systems. The units require a range of taste-masked materials and have more rapid disintegration than other tablet-based systems\textsuperscript{45}.

2. Compressed tablet-based systems

This system is completely based on standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration and packaging, which can range from standard HDPE bottles to more specialist pack designs for product protection\textemdash for example- CIMA Labs’, PackSolv\textsuperscript{46}. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by using water soluble excipients, super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach is BiovailsFuisz technology. It uses the Shearform system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer time to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology, branded companies and generic pharmaceutical companies, for development of fast-dissolve dosage forms\textsuperscript{47}.
3. Oral Thin Films (OTF)
Oral films, also called oral wafers, which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become advanced in fast-dissolve pharmaceutical drug delivery.

Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years and in the oral care markets in the form of breathe strips and became a novel and accepted form by consumers for delivery of vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for Transdermal drug delivery capitalized this technology to OTF formats. Today, OTFs are a accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to middevelopment stages for prescription drugs.

This is largely the success of the consumer breath freshener products such as Listerine Pocket Packs in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film. This film can incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into dosage units for packaging in pharmaceutically acceptable formats.

Table 1: Types of wafers and their properties

<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 (cm²)</td>
<td>2-8</td>
<td>2-7</td>
<td>2-4</td>
</tr>
<tr>
<td>Thickness(µm)</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</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>Site of action</td>
<td>Systemic or local</td>
<td>Systemic or local</td>
<td>Systemic or local</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>
</tbody>
</table>
**Classification of Oral Film**

There are three different subtypes

1. Flash release,
2. Mucoadhesive melt-away wafer,

These three types of oral films are differentiated from each other in following table 1.

**Advantages of Oral Thin Film**

1. This dosage form has some advantages over other oral formulations such as-
2. Availability of large surface area that leads to the rapid disintegration and dissolution in oral cavity.
3. The disadvantage of most ODT is that they are fragile and brittle which needs special package for protection during storage and transportation. Since the films are flexible there is ease of transportation, consumer handling and storage.
4. As compared to drops or syrup formulations, precision in the administered dose is ensured for each of the strips.
5. Pharmaceutical companies and consumers preferred OTFs as accepted alternative to traditional medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need of water.
6. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass metabolism. This advantage can be exploited in preparing products with improved oral bioavailability.
7. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects.
8. Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
9. OTFs disintegrate on a patients tongue in a few seconds for the rapid release of one or more APIs. The formulation of dissolvable films is facilitated through aqueous polymer matrices with high molecular weight (MW), and provides flexibility to achieve certain physical properties.
10. Beneficial in cases such as motion sickness, acute pain, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required\(^{60}\).
11. 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.

12. 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.

13. Provide new business opportunity like product differentiation, product promotion, patent extension\textsuperscript{50}.

**Disadvantage of Oral Strip**

The disadvantage of Oral Strip is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active ingredient can be improved up to 50% per dose weight\textsuperscript{51}. Novartis Consumer Health's Gas-X\textsuperscript{®} thin strip has a loading of 62.5 mg of simethicone per strip\textsuperscript{61}. There are number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these are best suited to lower-dose products. For example, Labtec claim that the Rapid Film technology can incorporate dose of up to 30 mg. The other challenge with these dosage forms is achieving Dose Uniformity\textsuperscript{61}.

**Special features of mouth dissolving films**

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release\textsuperscript{9}

**The ideal characteristics of a drug to be selected**

- The drug should have pleasant taste.
- The drug should have low dose upto 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug with good stability and solubility in water and in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue\textsuperscript{10}.
Table 2: Comparison between orally fast dissolving films and oral disintegrating tablets\textsuperscript{11}.

<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</td>
<td>Lesser dissolution due to</td>
</tr>
<tr>
<td>larger surface area</td>
<td>less surface area</td>
</tr>
<tr>
<td>Better durable than oral</td>
<td>Less durable as compared with oral films</td>
</tr>
<tr>
<td>disintegrating tablets</td>
<td></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>

STRUCTURAL FEATURES OF ORAL MUCOSA

Structure

The outermost layer of the oral mucosa is the stratified squamous epithelium. Beneath this lies a basement membrane, which is a lamina propria followed by the sub mucosa as the innermost layer. The epithelium layer is similar to that of 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\textsuperscript{16}. The turnover time for the buccal epithelium has been estimated for about 5-6 days and this is representative of the oral mucosa as a whole. The thickness of oral mucosa varies depending upon the site: such as the buccal mucosa measures about 500-800 µm, whereas the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measures about 100-200 µm. The epithelium composition also varies depending upon the site in the oral cavity. The mucosa of the gingivae and hard palate are keratinized which are similar to the epidermis which contains ceramides and acylceramides (that are neutral lipids) which have been found to be associated with the barrier function. The mucosal layer of the soft palate, the sublingual and the buccal regions, however, are not keratinized and relatively impermeable to water and have only small amounts of ceramides\textsuperscript{17-19}. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosylerceramides. The non-keratinized epithelial layer have been found to be more permeable to water than keratinized epithelia\textsuperscript{17-20}.
Permeability

The above figure represents the layers of oral mucosa from outside to innermost. In general in terms of permeability the oral mucosa is intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is about 4-4000 times greater than that of the skin. It has been assumed that there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.

The permeation enhancer plays an important role in oral region or the better absorption of APIs. So there is need of permeation enhancer in case of drugs that are absorbed orally where the drug is released from the formulation. Some of the examples of permeation enhancers are:

- Aprotinin
- 23-lauryl ether
- Azone
- Benzalkonium chloride
- Cetylpyridinium chloride
- Cyclodextrin
- Dextran sulphate
- Menthol
- Sodium glycodeoxycholate
- Sodium taurodeoxycholate
Composition of oromucosal region

The oromucosal cells are mainly made up of proteins and carbohydrates. It acts as a lubricant and adhesive in nature, allowing cells to move freely relative to one another with less friction\textsuperscript{41}. The mucus present is also believed to play an important role in bio adhesion of mucoadhesive drug delivery systems\textsuperscript{42}. In the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva whereas in other parts of body mucus is synthesized and secreted by the goblet cells. The 70% of the total mucin found in saliva is contributed by the minor salivary glands\textsuperscript{41-43}.

Another important feature of the oral cavity is the presence of saliva (contributes to digestive secretion) produced mainly by the three pairs of salivary glands such as (parotid, submandibular and sublingual glands). Saliva is mostly water contributing of 1% organic and inorganic materials. The digestive enzyme which is present in saliva is the salivary amylase, which helps in breaking down starch molecules to shorter chains of glucose molecules. The Saliva contains many of the chemicals that are found in plasma as the saliva is made from blood plasma.

The flow rate is the major determinant of the salivary composition which in turn mainly depends upon three factors: that is the time of day, the type of stimulus and the degree of stimulation\textsuperscript{41-43}. The pH of saliva ranges from 5.5 to 7. The daily production of salivary volume ranges between 0.5 to 2 litres and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. The main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

**FORMULATION CONSIDERATION\textsuperscript{12}**

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Surfactants
- 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 and variety of APIs can be delivered through fast dissolving films. Small dose molecules are 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 useful to have micronized API which will improve the texture of the film and gives better dissolution and uniformity in the OFDFs. Many APIs, are bitter in taste which are potential candidates for this technology\textsuperscript{80}. This makes the formulation unpalatable especially for pediatric preparations, so the API should be taste masked with sweeteners. Various methods can be used to improve the palatability. Among those, the simplest one involves the mixing and co-processing of API with excipients with pleasurable taste and termed as obscuration technique\textsuperscript{13}.

Table 3: 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>

Film forming polymer
The final thin film that is used must necessarily be water soluble as it should be disintegrated in saliva. To prepare a thin film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property\textsuperscript{53}.

The polymer should exhibit sufficient peel, shear and tensile strengths. It should be readily available and should not be very expensive. The polymers can be used alone or in combination to improve hydrophilicity, flexibility, mouthfeel and solubility characteristics of fast dissolving films\textsuperscript{81}.

The stiffness of the strip depends on the type of polymer and the amount of polymer in the formulation. Polyvinyl pyrrolidone films are brittle in nature and so co-povidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating films. Combination of microcrystalline cellulose and maltodextrin can be used to formulate fast dissolving films.
of piroxicam by hot melt extrusion technique. In this case, microcrystalline cellulose is used to achieve the film non-sticky, smooth and also used to decrease the disintegration time, improve the dissolution of drug from the films. Water soluble polymer include natural gums such as those derived from guar, xanthum, acacia, Arabic or tragacanth, other available polymers are, polyethylene oxide, acrylic based polymer and several types of sodium carboxymethyl cellulose (CMC), several types of hydroxypropyl methyl cellulose (HPMC), a synthetic copolymer of polyethylene glycol–polyvinyl alcohol (Kollicoat IR) and sodium alginate. Cellulose ethers are widely available. Pullulan, an α-1,6-linked maltotriose produced from the fungus Aureobasidium pullulans, has also been used. Five starches and maltodextrin have investigated as alternative film formers. The physicochemical characteristic of the polymers selected for film formulation play a vital role in determining the disintegration time of thin film oral dosage form.

**Plasticizer**

Plasticizer is a vital ingredient of the fast dissolving films which help to improve the flexibility of the strip and reduces the brittleness of the films. It improves the film forming 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 in the casting of film. 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.

Typically the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight. Inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. The use of certain plasticizers may also affect the absorption rate of the drug.

**Surfactants**

Surfactants act as solubilizing or wetting or dispersing agent in formulation so that the film gets dissolved within seconds and release active agent quickly. Some of the commonly used surfactants are sodium lauryl sulphate, benzalkonium chloride, tweens etc. One of the most important surfactant is poloxamer 407 that is used as solubilizing, wetting and dispersing agent.
Sweetening agents

Sweeteners are important part of the formulation intended to be disintegrated or dissolved in the oral cavity. 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 fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they provide good mouth-feel and cooling sensation. However the use of natural sugars in such preparation needs to be restricted for 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 sucralose have more than 200 and 600 time sweetness. Neotame and alitame 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 are used in the suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron respectively.

Saliva stimulating agent

The saliva stimulating agents is used to increase the rate of production of saliva that would aid in the faster disintegration of the 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.

Flavoring agents

Preferably up to 10%w/w flavors are added in the OFDF formulations. The acceptance of the oral dissolving formulation 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 used in the formulation. Age plays a significant role in the taste fondness. The geriatric 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 and can be used alone.
or in the combination\textsuperscript{87}. 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\textsuperscript{88}.

**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\textsuperscript{89}.

**METHOD OF PREPARATION**

One or more of the following process can be used combinely to manufacture the mouth dissolving films.
1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling\textsuperscript{52}

1. **Solvent casting method**

In solvent casting method excipients are dissolved in water. Then water soluble polymers are added and dissolved. At last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried\textsuperscript{54}.

```
Water / suitable solvent + Excipients
Heated upto 60\degree c  \rightarrow\quad Stirred at 1000rpm
Solution + Add Polymers
Cooled to room temp  \rightarrow\quad Stirred at 1000rpm
Add Drug
Stirred until to form homogeneous solution
Dried on petry dish
Film is formed
```

**Figure 2:** Flow chart of solvent casting method for the preparation of fast dissolving films
Advantages

- Better uniformity of thickness and better clarity than extrusion.
- Film has fine gloss and freedom from defects such as die lines.
- Film has more flexibility and better physical properties. The preferred finished film thickness is typically 12-100 µm, although various thicknesses are possible to meet API loading and dissolution needs.<sup>55</sup>

Disadvantages

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.<sup>56</sup>

2. Semisolid casting

This method is adopted when acid insoluble polymers are to be used. Add solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide gel mass is obtained. 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.<sup>57</sup>

3. Hot melt extrusion

In hot melt extrusion method the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder and screw speed should set at 15 rpm to process the granules inside extruder for approximately 3–4 min. The processing temperatures should be 80<sup>0</sup>C (zone 1), 115<sup>0</sup>C (zone 2), 100<sup>0</sup>C (zone 3) and 65<sup>0</sup>C (zone 4). The extrudate (T = 65<sup>0</sup>C) then pressed into a cylindrical to obtain a film.<sup>58</sup>

Advantages

- Without use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.<sup>59</sup>
Disadvantages

- Thermal degradation due to use of high temperature
- Flow properties of the polymer are essential to processing
- Limited number of available polymers
- All excipients must be devoid of water or any other volatile solvent

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.

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
Mechanical properties

**Thickness**: As the thickness of film is directly proportional with drug content uniformity so it is necessary to maintain uniformity in the thickness of the film. It can be measured by screw gauge or calibrated digital Vernier Calipers at different strategic locations.\(^\text{71}\)

**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 to evaluate pharmaceutical OFDF. 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.\(^\text{62}\)

**Tensile strength**: Tensile strength is the maximum stress applied to a point at which the strip 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.\(^\text{72}\)

\[
\text{Tensile Strength} = \frac{\text{Load at failure}}{\text{Film thickness} \times \text{Film width}} \times 100
\]

**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.\(^\text{73}\)

\[
\text{Percent Elongation} = \frac{L}{L_0} \times 100
\]

L = Increase in length of film

L\(_0\) = Initial length of film

**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:

\[
\text{Young's Modulus} = \frac{\text{Slope}}{\text{Film thickness} \times \text{Crosshead Speed}} \times 100
\]
Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation\(^74\).

**Tear resistance:** Tear resistance of plastic film or sheeting is a complex function of its resistance to rupture. Basically very low rate of loading 51 mm (2 in)/min is employed and is 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 strip is recorded as the tear resistance value in Newtons (or pounds-force)\(^75\).

**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 said as the folding endurance value\(^76\).

**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\(^77\).

**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 reported\(^78\).

**Swelling index:** It is useful in case of film formulation having gelling property and measured by 2 methods.

1. **Linear expansion coefficient in water**
   Film is immersed in water. Specimen is taken 2, 4, 6, 8, 10, 15, 30 and 60 seconds and the size of side length is measured. It is calculated as:

   \[
   \text{L}% = \frac{L_1 - L_0}{L_0} \times 100
   \]

   Where:
   
   L1 = Side length after immersion
   L0 = Side length before immersion
2. Amount absorbed in purified water

The film is weighed (W1) and put into the stainless steel mesh basket. The weight after immersion in water is measured (W2). Similarly, weight after immersion of basket without film (W3). The amount absorbed (W) is determined by the following equation

\[ W = \frac{W_2 - W_1 - W_3}{W_1} \]

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

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

Where T600 is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

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. 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 strips.

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.

Contact angle measurement: Time dependent contact angle is measured by an optical contact angle meter. The Contact angle is measured by different methods like the two tangential methods, a height width ratio, the circle fitting and sessile drop fitting.
Table 4: 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>

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