



Review Article

## FAST DISSOLVING ORAL FILMS: A NOVEL TREND TO ORAL DRUG DELIVERY SYSTEM

Mukem Bhattarai<sup>1</sup>, Amit Kumar Gupta<sup>1\*</sup>

Department Of Pharmacy, Sunsari Technical College, Tribhuvan University, Dharan<sup>1</sup>

\*Corresponding author email: [amitknepal@gmail.com](mailto:amitknepal@gmail.com)

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### Abstract

Oral routes are most commonly preferred route for delivering drug. Most common oral dosage forms are tablet and capsules. But many patients such as geriatric, pediatric and dysphasic patients find difficult to swallow conventional tablet and capsule. To overcome various problems related to swallowing, Fastdissolving Tablets (FDTs) were designed in early 19th century and hence further advancement has led to development of Fast Dissolving Oral Films (FDOFs). In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. Amongst the plethora of avenues explored for rapid drug releasing product, FDOFs technology is gaining much attention. These are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or mastication. This technology has been used for local action as well as rapid release products. The fast dissolving oral films are formulated using various Active pharmaceutical ingredients (API), film forming polymers, plasticizer, flavors, colors and sweeteners. Initially FDOFs are up to breath strips, confection and oral care markets. But now it became a novel and widely accepted technology for delivering OTC and prescription medication too.

**Keywords:** Geriatric, Pediatric, Dysphasic, Fast Dissolving Oral Film, Disintegrate, OTC (over the counter), Prescription.

### INTRODUCTION

The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance. Oral dosage forms are more popular than other dosage forms because of ease of administration, accurate dosage, self-medication, pain avoidance, patient compliance, etc.<sup>[1]</sup> Despite of tremendous advancement in drug delivery the oral route of drug administration is the most important method of administration of drug for systemic effect.<sup>[2]</sup> Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability by patients. About 60% of all dosage forms available are the oral solid dosage form. The lower

bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenteral and liquid orals. But the liquid orals (syrup, suspension, emulsion etc.) have the problem of accurate dosing mainly and parenteral are painful drug delivery, which may cause patient non-compliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance.<sup>[3]</sup> The most popular solid dosage forms are tablet and capsules. Many patients find it difficult to swallow tablets and hard gelatin capsules particularly geriatric and pediatric patients and do not take their medicine as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of general population. In some cases such as motion sickness, sudden episode of allergic attack or coughing, fear of choking and an unavailability of water,

the swallowing of tablet and capsule become difficult<sup>[4]</sup>. To overcome various problems related to swallowing, fast dissolving Tablets (FDTs) were designed in early 19th century.

The first Orally Dispersible Tablet (ODT) form of a drug to get approval from the U.S Food and Drug Administration (FDA) was Zydis ODT, a formation of Claritin (Loratadine), in December 1996.<sup>[5]</sup> This has slowly led to their further advancement and thus Fast Dissolving Films (FDFs) were developed. Chloraseptic® Relief Strips™ were the first oral thin-film product to incorporate a drug and were introduced in the United States in September 2003 by Prestige Brands International for relief of sore throat.<sup>[6]</sup> The first oral soluble film approved by the US FDA as a prescription medication is Zuplenz (ondansetron) oral soluble film for the prevention of postoperative, highly and moderately emetogenic cancer chemotherapy-induced, and radiotherapy-induced nausea and vomiting which is the product of Strativa Pharmaceuticals, the proprietary products division of Par Pharmaceuticals in July 2, 2010.<sup>[7]</sup>

Fast dissolving dosage form has become increasingly important because of their unique properties. They quickly disintegrate and can be administered without water, making them particularly suitable for pediatrics and geriatric patients. Fast dissolving films have gained popularity not only in breath strips but also in personal care, food and drug delivery markets.<sup>[8]</sup>

Oral thin films markets are shifted from primarily over the counter product to a prescription product focused market. Many of prescription oral thin films have been approved in the United State, Europe and Japan. Reckitt Benckiser's Suboxone (buprenorphine and nalaxone) thin film sales reached \$513 million in 2011. Technology catalysts forecast the future growth of OTF with key APIs will reach up to \$1 billion in 2015.<sup>[9]</sup> This is largely as a result of the success of the consumer breath freshener products such as Listerine Pocket Paks® in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats.<sup>[10]</sup>

### **Fast dissolving oral film**

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel

and widely accepted form by consumers for delivering vitamins and personal care products.<sup>[11]</sup>

Today, Oral Thin Films are a proven and accepted technology for the systemic delivery of active pharmaceutical ingredients (APIs) for over-the-counter (OTC) medications and some prescription drugs.

Fast dissolving films, 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; then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.<sup>[12]</sup>

Fast dissolving oral film is prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Fast dissolving oral film has emerged an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and OTC medications. Similar in size, shape and thickness to a postage stamp thin-film strips are typically designed for oral administration, with the user placing the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal). These drug delivery options allow the medication to bypass the first pass metabolism thereby making the medication more bioavailable. As the oral thin film dissolves, the drug can enter the blood stream through enteric, buccal or sublingually.<sup>[13]</sup>

### **Features of fast dissolving oral films**

This delivery system consists of a thin film shape and size like postage stamp. Fast dissolving oral films dissolves in the mouth like a cotton candy leaving pleasant mouth feel and acceptable taste. Fast dissolving oral film is unobstructed. After placing it on the top of the tongue, the film dissolves within seconds, by passing first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug. Fast dissolving oral film should leave minimum or no residue in the mouth after oral administration. Fast dissolving oral film should exhibit low sensitivity to environmental conditions such as temperature and humidity.

### **Advantages of fast dissolving oral films**

The accessibility of the larger surface area that lead to quick disintegration and dissolution disintegrate and dissolution in the oral cavity within seconds.<sup>[14]</sup> The disadvantage of most Oro Dispersible Tablet is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the Oro Dispersible Tablets. Hence, there is ease of transportation and during consumer handling

and storage. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.<sup>[15]</sup> 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. The dosage form can be consumed at any place and any time as per convenience of the individual.<sup>[16]</sup> Pharmaceutical companies and consumers alike have embraced Oral Thin Films as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. Oral Thin Films offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.<sup>[17]</sup> The formulation of dissolvable films is customarily facilitated through aqueous polymer matrices that span a wide molecular weight (MW) range, thereby providing flexibility to achieve certain physical properties.<sup>[18]</sup>

**Disadvantages of fast dissolving oral films**

The dose uniformity is a technical challenge. They are also hygroscopic in nature. They have high dose cannot be incorporated into the strip. 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 film has a loading of 62.5 mg of simethicone per strip.<sup>[18, 19]</sup>

**Classification of Oral Film<sup>[20]</sup>**

*Table 1.Types of flim and their properties*

Property/ Subtype	Flash Release Wafer	Mucoadhesive melt away wafers	Mucoadhesive sustained release
Area (cm <sup>2</sup> )	2-8	2-7	2-4
Thickness(µm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer system	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	Low/Non soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution

Application	Tongue(upper plate)	Gingival or buccal region	Gingival
Dissolution	Maximum 60 seconds	Disintegration in few minutes, forming gel	Maximum 8-10 hours

**Formulation aspects for fast dissolving oral films**

Formulation of FDOFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of oral film should be Generally Regarded as Safe (i.e.GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

*Table 1.Generalized detail of different ingredients of fast dissolving oral films<sup>[16]</sup>*

S.No	Ingredients	Amount (w/w)
1.	Drug (API)	5-30%
2.	Water soluble polymer	40-50%
3.	Plasticizer	0-10%
4.	Saliva stimulating agents	2-6%
5.	Sweetening agents	3-6%
6.	Surfactant	Q.S
7.	Flavors, colors, Fillers	Q.S

**Active Pharmaceutical Ingredients**

The fast dissolving oral film technology has potential for delivery of variety of APIs. Since the size of the dosage form is limited, high dose of molecules are difficult to be incorporated into the films. A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in FDOFs. Multivitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds<sup>[21]</sup>

Suitable candidate for fast dissolving oral film are 1. Drug should be potent having low dose, 2. Drug should have no bitter taste, 3. Good stability in water and pH of saliva and permeable through buccal mucosa. Many APIs that can be potentially used for film technology are with bitter taste

which makes the formulation unpalatable especially for pediatrics formulation. This leads to the very significant unit operation- taste masking before incorporating the API in the fast dissolving oral films. Various methods can be used to improve palatability of the formulation such as:

**Obscuration Technique:** The simplest method involves the mixing and blending of bitter tasting APIs with excipients of acceptable taste.

**Barrier Technique:** This method includes complexation, polymeric coating, and conversion into micro particles or microcapsules, coated particles or coated granules.<sup>[22]</sup>

Various categories of drug such as cardiovascular , antiemetic ,analgesics, ant allergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, anti-Alzheimer's, expectorants, anti-tussive can formulated as film.<sup>[23]</sup>

### **Film forming polymers**

Fast dissolving Film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. "Water soluble polymers" are used as film formers for fast dissolving films. The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases.<sup>[24]</sup>

Some of the water soluble polymers used as film former are HPMC E3, E5 and E15 and K-3 ; Methyl cellulose A-3, A-6 and A-15; Pullulan; carboxymethylcellulosecekol 30; Polyvinylpyrrolidone PVP K-90; Pectin; Gelatin; Sodium Alginate; Hdroxypopylcellulose; Polyvinyl alcohol; Maltodextrins and Eudragit RD 108, 9, 10, 11, 12 ; Eudragit RL100. Polymerized rosin is a novel film forming polymer.<sup>[25, 26]</sup>

### **Ideal properties of the film forming polymers**<sup>[8, 24]</sup>

- The polymer employed should be non-toxic, nonirritant and devoid of leachable impurities.
- It should have good wetting and spread ability property.
- The polymer should exhibit sufficient peel, shear and tensile strengths.
- The polymer should be readily available and should not be very expensive.
- It should have good shelf life.
- It should not aid in cause secondary infections in the oral mucosa/ dental region.
- It should have a good mouth feel property.

### **Plasticizer**

The role of Plasticizer is beneficial for preparation of FDF. Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the film. The plasticizer should be compatible with polymer and solvent. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer.<sup>[27]</sup> Propylene glycol (PG), Poly ethylene Glycol (PEG), Glycerol, 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. Plasticizer may lead to film cracking, splitting and peeling of the film .It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.<sup>[28, 29]</sup>

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 40–60 °C for non-aqueous solvent system and below 75 °C for aqueous systems.<sup>[30, 31]</sup>

Plasticizer should be compatible with drug as well as other excipients used for preparation of strip. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both Hypromellose as well as polyvinyl alcohol films.<sup>[21]</sup> Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid.<sup>[32]</sup>

### **Saliva stimulating agent**

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. 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. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.<sup>[33]</sup>

### **Sweetening agent**

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. Suitable sweeteners include: (a) water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose and stevioside, etc (b) water soluble artificial sweetener: sodium or calcium saccharin salts, cyclamate salts and acesulfame-k, etc (c) Dipeptide based

sweetener: aspartame (d) protein based sweeteners: thaumatin I and II. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Generally sweeteners are used in the concentration of 3 to 6 % w/w either alone or in combination.<sup>[14, 22]</sup>

### Surfactant

Surfactants are used as solubilizing or wetting or dispersing agent so that the films gets dissolve within seconds and release the active agent instantly. Several numbers of surfactants are used in oral strip. One of the most important surfactant is poloxamer 407 that is used as solubilizing, wetting and dispersing agent.<sup>[12]</sup> Sodium lauryl sulfate is used in the formulation of mouth dissolving film of amlodipine.<sup>[34]</sup>

### Flavors

These are most important agents which are to be added to the pharmaceutical oral preparations because flavors are the ultimate goal for the choice of the preparations by the patients. It might have become the important factor for the sale of products. Both natural and artificial flavor are used. 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. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.<sup>[35]</sup>

### Colors

A full range of colors is available, including FD&C colors, EU Colors, Natural Colors and custom Pantone matched colors.<sup>[36]</sup> Pigments such as titanium dioxide or FD & C approved coloring agents are incorporated (not exceeding concentration levels of 1 percent; w/w) in Oral film when some of the formulation ingredients or drugs are present in insoluble or suspension form.<sup>[37]</sup>

### Method of preparation of fast dissolving films

Fast dissolving films can be prepared by:

- a. Solvent casting method
- b. Semisolid casting method
- c. Hot melt extrusion
- d. Solid dispersion extrusion
- e. Rolling method

#### a. Solvent casting method<sup>[7, 37]</sup>

In this method, water soluble polymers are dissolved in suitable solvent and the drug along with other excipients is dissolved in suitable solvent. Then both the solutions are mixed and stirred. This solution is then degassed under vacuum to settle the air bubbles. This bubble free solution is then finally casted into Petri plate and dried.

#### Advantage

- Great uniformity of thickness and great clarity than extrusion.
- Films have fine gloss and free 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.

#### b. Semisolid casting method:<sup>[10, 38]</sup>

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.

#### c. Hot melt extrusion:<sup>[39, 40]</sup>

Hot melt extruder is used in this process. This technique involves shaping a polymer into a film via the heating process. A blend of pharmaceutical ingredients including API in dry state is filled in the hopper, conveyed, mixed and subjected to the heating process, and then extruded out in molten state melted by the extruder. The molten mass thus formed is used to cast the film. A critical step is the casting and drying process. This technique has many advantages, such as this process involves lower temperature and shorter residence times of the drug carrier mix, absence of organic solvents, continuous operation possibilities, minimum product wastage, good control of operating parameters and possibilities to scale up.

#### Advantages

- Improved bioavailability of poorly soluble compounds.

- During Processing solvents and water are not required.
- Cost-effective process with reduced production time and reduced number of unit operations.
- Homogeneous distribution of fine particle occurs.
- Sustained modified and targeted release capability.
- Superior stability at varying pH and moisture levels.
- Better content uniformity was obtained among granules of different size ranges.

#### **Disadvantages**

- Thermal degradation due to use of high temperature.
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers.
- Require high power input.
- All excipients must be devoid of water or any other volatile solvent.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
- Higher-melting-point binders require high melting temperatures and can contribute to volatility problems especially for heat-labile materials.

#### **d. Solid dispersion:**<sup>[7, 16]</sup>

The term solid dispersion refers 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 drugs are dissolved in suitable solvents and then solutions are incorporated into the melt of polyethylene glycol below 70° C. Then solid dispersions are finally shaped into the films by means of dies.

#### **e. Rolling Method:**<sup>[41]</sup>

In rolling method, a solution or 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 cut in to desired shapes and sizes. 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.

#### **Patented Technologies:**<sup>[42]</sup>

##### **a. XGel:**

XGel is at the heart of Meldex international's intellectual properties used in all its film system and its ingestible delivery technologies. XGel film Technology developed by

BioProgress is bringing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry. X Gel film, potentially enhance the product stability. It has also been developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices. The development and manufacture of XGel films uses a means called "solution casting".

##### **b. Soluleaves:**

In this technology, the film is produced in order to release the active ingredients on coming in contact with saliva. This is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. Soluleaves technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as nutritional products. Soluleaves films can also be designed to adhere to mucous membranes and to release the active ingredients slowly over 15 minutes.

##### **c. Wafertab:**

Wafertab is a drug delivery system that incorporates pharmaceutical actives into ingestible films. It is a patented delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting. Wafertab system lends itself to many possibilities for innovative drug design, enabling multiple films with different actives to be bonded together.

##### **d. Foamburst:**

Foamburst is a patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific tasteburst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt in-the mouth sensation. Foamburst has attracted from and confectionary manufactures as a mean of carrying and releasing flavors.

##### **e. Micap:**

Micap signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress water-soluble films. The developments aimed at providing new delivery mechanisms for the \$1.4bn global market for smoking cessation products (SCPs).

#### **Pharmacopoeial Status of Oral Films:**<sup>[43]</sup>

Monographs of common dosage forms are provided by the pharmacopoeias (e.g. Ph. Eur., USP). Even though dosage forms for application in the oral cavity such as Medicated chewing gums, Oromucosal preparations, Orodispersible tablets or oral Lyophilisates are included, monographs and specifications for oral films of diverse dissolution kinetics has not yet been established. There are inadequate pharmaceutical technical procedures for analysis in development and quality control of oral films as well. For instance, disintegration and dissolution testing procedures may be provided, but the recommended conditions such as volumes of media do not reflect the natural conditions in the oral cavity.

**Evaluation of fast dissolving oral films:** [44-49]

**a. General appearance:**

The fast dissolving films are evaluated by visual observation such as transparent and semitransparent nature of strip.

**b. Weight of films**

Oral fast dissolving films can be weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and APIs.

**c. Organoleptic evaluation:**

Color is vital means of identification for many pharmaceuticals products and is also usually important for consumer acceptance. The color of the product must be uniform within the dosage form. Odor is also important for consumer acceptance of oral dosage form and can provide an indication of the quality of the films as the presence of an odor in a batch could indicate a stability problem. However the presence of an odor may be characteristic of the drug (e.g. vitamins), added ingredients (e.g. flavoring agents), etc. Taste is an also essential factor for the consumer acceptance and many companies utilize taste panels to judge the preference of different flavors level in the development of product. 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 are being used for this purpose.

**d. Thickness:**

A thickness of film should be measured with the help of micrometer screw gauge or calibrated digital vernier calipers. Film should be measured at five points i.e. from the center and from all the four corners and then mean thickness is calculated. It is necessary to determine the uniformity of

thickness as it is directly related to accuracy of dose in the film.

**e. Mechanical properties**

Three mechanical properties namely tensile strength, tear resistance, Young's modulus and percentage elongation are calculated.

**Tensile strength:** Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by formula:

$$\text{Tensile strength} = \frac{\text{Load at failure} * 100}{\text{Film thickness} * \text{film width}}$$

**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.

$$\text{Percent elongation} = \frac{L}{L^0} * 100$$

L = Increase in length of film

L<sup>0</sup> = Initial length of film

**Young's Modulus:**

Young's modulus or elastic modulus is the measure of stiffness of film. It is expressed as the ratio of applied stress over straining the region of elastic deformation as follows:

$$\text{Young's Modulus} = \frac{\text{Slope} * 100}{\text{Film thickness} * \text{crosshead speed}}$$

Brittle and Hard film demonstrates a high tensile strength and Young's modulus with small elongation.

**f. Folding endurance**

It is determined by folding the films of uniform cross sectional area and thickness at the same place repeatedly until it breaks.

**g. Disintegration time**

The disintegration time is noted which is the time when the film starts to break or disintegrates. The Disintegration test was carried out in 10 ml phosphate buffer (pH 6.8) in a beaker at 37±0.5 °C.

**h. pH value:**

P<sup>H</sup> is measured by the dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution should have nearly uniform pH value.

**i. 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 preset time interval until constant weight was observed.

$$\text{Degree of swelling} = \frac{W_t - W_o}{W_o}$$

Where, W<sub>t</sub> is weight of film at time t, and W<sub>o</sub> is weight of film at time zero

**j. Stability Studies:**

Stability studies on the optimized oral fast dissolving film is carried out for determination of effect of temperatures and humidity on the stability of the drug. The film are stored in an aluminum foil and subjected to stability at room temperature. The sample can withdraw at 3 months and 6 months and subjected for cumulative % drug release and in vitro dissolution studies to determine disintegration time and disintegration test.

**k. Assay/Uniformity of drug content:**

This parameter can be determined by dissolving known weight of film by homogenization in 100 ml of simulated saliva of pH 6.8 for 30 min with continuous shaking. Then assay is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Determination of content uniformity is done by estimating the API content in individual strip. Limit regarding to content uniformity is 85-115%.

**l. Dissolution test:**

Dissolution is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent concentration. Dissolution testing can be performed in simulated saliva solution or pH 6.8 phosphate buffers 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.

**m. Packaging:** <sup>[50, 51]</sup>

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three rapid films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics:

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement
- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product tastes or odors.

**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:**

The blister container 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 blister package is formed by heat –softening a sheet of



thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mold. After cooling the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

**Barrier Films:**

Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. 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.

*Table 3: Some of the fast dissolving films which are available in market are listed below.*<sup>[19, 21, and 42]</sup>

Brand name	Manufacturer / Distributor	API (strength)	Uses
Klonopin wafers	Solvay Pharmaceuticals	Clonazepam ( in five strength; 0.125mg, 0.5mg, 1mg &2mg)	Anxiety
Listerine Cool Mint Pocket Paks	Pfizer, Inc	Cool mint	Mouth fresheners
Sudafed	WoltersKuwert Health Inc	Phenylephrine	congestion
Suppress	Innozen, Inc	Menthol (2.5mg)	Cough suppressant
Triaminic	Novartis	Diphenhydramine HCL(12.5)	Anti-allergic
Theraflu	Novartis	Dextromethorphan HBR (15mg)	Cough suppressant
Orajel	Del	Menthol/pec	Mouth

		tin (2mg/30mg)	ulcer
Gas-X	Novartis	Simethicone 62.5mg	Anti Fluctuating
Chloraseptic	Prestige	Benzocaine/menthol(3mg/3mg)	Sore throat
Benadryl	Pfizer	Diphenhydramine HCL(12.5mg or 25 mg)	Anti-allergic

**CONCLUSIONS**

Recently pharmaceutical companies embraced fast dissolving films as a practical and accepted alternative to traditional medicines. The unique properties of FDOFs such as easy administration, quickly disintegration, consumer preference, rapid action, etc making it as a useful delivery form of medication intended for geriatric, pediatrics or dysphasic patients who have difficulty in swallowing tablets and capsule. This technology is also a good tool to pharmaceutical company for product life cycle management for increasing the patent life of existing products. These combined potentials lead to pave way for shifting primarily OTC product to prescription product. The FDOFs bridges the gap between consumer preferences and manufacturer. Hence within the patient population and formulators fast dissolving oral films leads to be an ideal dosage form. This review is an effort to combine the knowledge available in fast dissolving oral films.

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