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FAST DISSOLVING ORAL FILMS: A COMPREHENSIVE REVIEW

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ABSTRACT

In the late 1970s, rapid disintegrating drug delivery system was developed as an alternative to capsules, tablets and syrups for geriatric and pediatric patients having problems in swallowing. To overcome the need, number of orally disintegrating tablets which disintegrate within one minute in mouth without chewing or drinking water were commercialized. Then later, oral drug delivery technology had been improved from conventional dosage form to modified release dosage form and developed recently rapid disintegrating films rather than oral disintegrating tablets. Orally fast dissolving films (OFDFs) have been introduced in the market recently as they provide convenience and ease of use over other dosage forms such as orally disintegrating tablets. This technology 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, so OFDFs are gaining the interest of large number of pharmaceutical industries. Orally fast dissolving film is the type of drug delivery system which when placed in the oral cavity, disintegrate or dissolve within few seconds without the intake of water. OFDFs are very similar to postage stamp in their shape, size and thickness. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. Some companies introduced more robust forms of fast-dissolving drug delivery the film is placed on the top or the floor of the tongue. When put on the tongue, this film dissolves instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such case is enhancing drug bioavailability, No risk of chocking, Provide good mouth feel. The present review provides an account of various formulation considerations, method of preparation and quality control of the OFDFs.

KEYWORDS: Fast dissolving films, Oral strips, Tensile strength.

INTRODUCTION

Oral route is a most preferred route of drug administration for systemic effect due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability.[1,2] Tablet is the most preferred dosage form due to ease of manufacturing, transportation and more patient compliance.[3] Generally geriatric, pediatric, nauseous, bed ridden and noncompliance patients experience difficulties in swallowing the conventional oral dosage form and do not take their medicines as prescribed. It is estimated that 50 % of the population was affected by this problem, which finally results in a higher chance of noncompliance & ineffective therapy.[4] The elderly constitute a major portion of today's population mainly because of increased life expectancy of individuals.[5] Dysphagia or difficulty in swallowing is common problem, this disorder is coupled with several medical conditions including stroke, AIDS, thyroidectomy, Parkinson's disease, head and neck radiation therapy and other neurological disorders as well as encephalopathy.[6] The most common complaint with tablet is size, fear of chocking. The problem of swallowing tablets is more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.[7] To overcome this Oral fast disintegrating drug delivery systems were developed, these systems were initially developed within the late Seventies as an alternative to tablets, capsules and syrups for pediatric & geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. These dosage forms either dissolve or disintegrate generally within a 3 minute in mouth, without need of water. Oral fast Disintegrating dosage form have started gaining popularity & acceptance as new drug delivery system due to better patient compliance.[8]

Oral fast disintegrating dosage form consists of mouth dissolving tablets & fast dissolving films. Mouth dissolving tablets associated with many problems like leave residues in mouth which causes feeling of grittiness in mouth; there is a fear of choking, difficulty in swallowing tablets. To beat the issues of mouth dissolving tablets, a new drug delivery system for the oral delivery of the drugs, was investigated which is known as Fast dissolving films/oral dispersible film/ mouth dissolving films / oral disintegrating film/ oral dissolving film.[9] Fast dissolving oral film was developed based on the technology of the transdermal patches for oral delivery of drugs.[10] The delivery system consists of a thin film of the size of a postage stamp, which is placed on the patient's tongue or mucosal tissue, where it instantly hydrates by absorbing saliva; the film then rapidly disintegrates and dissolves to release the drug for oral mucosal absorption. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment.[11]

Fast dissolving drug delivery system

Fast dissolving drug delivery system is a new generation delivery system also known as fast dissolving/disintegrating film for the oral delivery of the drugs which came into existence in the late 1970's as an alternative to tablets, capsules, syrups and other formulations for pediatric and geriatric patients who experience difficulties in swallowing traditional solid dosage forms which combines both the advantages of conventional tablet and of liquid formulation.[12] FDDS is easy to administer and provides better patient compliance in the elderly, pediatric, mentally retarded, nauseated and uncooperative patients.[13] This delivery system consists of the solid dosage forms that dissolve quickly i.e. within a matter of seconds in the oral cavity without the administration of water. The delivery system consists of a very thin oral strip which is simply placed on the patient's tongue or any other oral mucosal tissue and instantly gets wetted by saliva.[14] The film rapidly hydrates onto the site of application. It then rapidly dissolves and disintegrates to release the medication for oro-mucosal absorption. Fast dissolving oral thin films are widely accepted by patients and also to the caregiver for their ease-of-delivery, portability and accurate dosing [15]. The robustness of the film depends upon the type and amount of polymer used and general dissolution time for orally dissolving film is 5–20 min. as per pharmacopoeia.[16,17] They also provide quick onset of action within few seconds as the oro-mucosal absorption of the drug occurs directly from the site of administration to the systemic circulation avoiding the first-pass metabolism to produce the desired effect.[18]

Anatomy of oral cavity

The structure and anatomy of oral cavity is studied for understanding the environment provided for delivering drugs [Fig. 1]. The oral mucosa allows direct access of drug to the systemic circulation and avoids first pass metabolism. The epithelium of the oral cavity is quite similar to that of the skin, with slight differences with regard to keratinization, protective and lubricant mucous which is spread across its surface.[19] The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral cavity is divided into two regions: outer being the oral vestibule bounded by the lips and cheeks; the hard and soft palates, the floor of the mouth and tonsils.[20] Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms.[21]

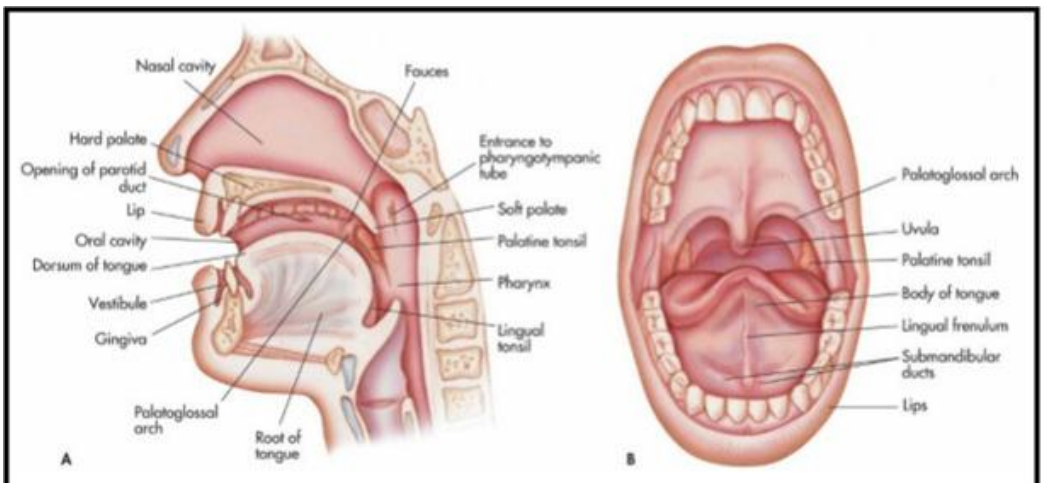
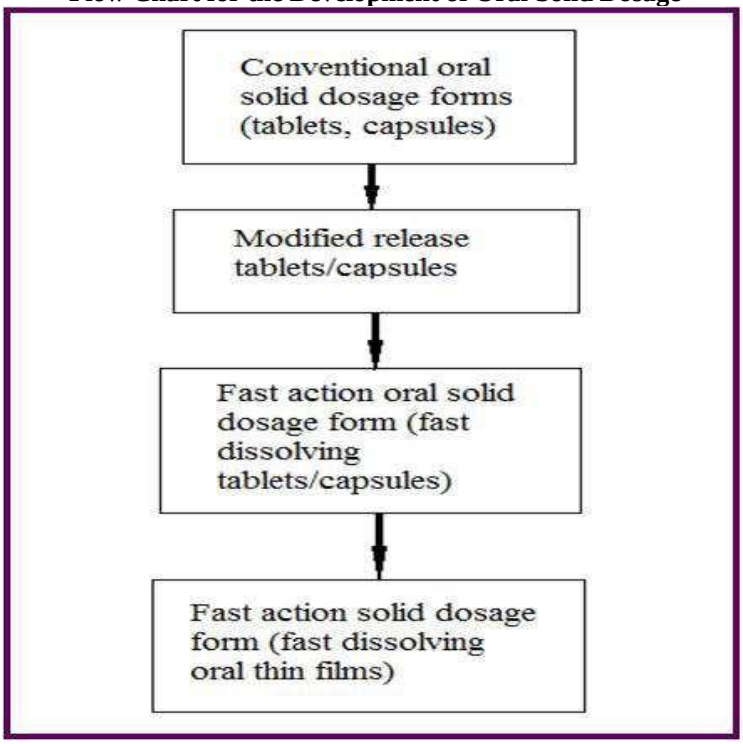


Figure 1: Anatomy of the oral cavity (http://baldaivirtuves.info/human-anatomy-mouth/human-anatomy-mouth-anatomy-mouth-oral-cavity-human-anatomy-library-physiology/)

Flow Chart for the Development of Oral Solid Dosage



Special Features of Fast Dissolving Oral Films[22,23]

1. Thin elegant film
2. Available in various size and shapes
3. Unobtrusive
4. Excellent mucoadhesion
5. Fast disintegration and dissolution
6. Rapid drug release
7. Bypasses first pass effect

Advantage of Orally Fast Dissolving Oral Films[24-27]

1. No need of water for administration.
2. Convenient for pediatric, geriatric and dysphasic patients having difficulty in swallowing.
3. Rapid disintegrating and dissolution in the oral cavity due to larger surface area of films.
4. Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect.
5. Reduce dose, enhances the efficacy and safety profile of the drug with reduced side effects.
6. Flexible and portable in nature so they provide ease in handling, transportation and storage.
7. Ease of administration to mentally ill, disabled, uncooperative patients and the patients who are on reduced liquid intake plans or are nauseated.
8. Beneficial in cases such as motion sickness, acute pain, sudden allergic attack, asthmatic attack and coughing, where an ultra rapid onset of action is required.
9. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed.
10. Accuracy in dose as compared to liquid formulations.
11. Pleasant mouth feel, leave negligible or no residue in the mouth after administration.

Limitations of Fast Dissolving Oral Films

1. High doses cannot be incorporated.
2. Excessive bitter drugs are not feasible.
3. Dose uniformity is a technical challenge.
4. They require special packaging for the products stability and safety.
5. Drugs which irritate the oral mucosa cannot be administered by this route.

The Ideal Characteristics of Drug To Be Selected.[24,27,28]

1. The drug should have pleasant taste. The drug should have small molecular size and low molecular weight.
2. The drug should have good solubility and stability in water as well as in saliva.
3. It should be partially unionized at the pH of oral cavity.
4. The drug should exhibit low sensitivity to environmental conditions.
5. It should have the ability to permeate oral mucosal tissue.
6. The therapeutic dose of the drug should not be greater than 40mg.

Research and development in the oral drug delivery system has led to transition of dosage forms 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). The Comparison between Fast Dissolving Oral Films and Fast Dissolving Tablets was given table 1.

Table 1: Comparison between Fast Dissolving oral Films and Tablets.[29,30]

Sl. No.	Oral Disintegrating Tablets	Orally Dissolving Films
1	It is a tablet	It is a film
2	Lesser dissolution due to less surface area	Greater dissolution due to larger surface area
3	Less durable as compared with oral films	Better durable than oral disintegrating tablets
4	Less patient compliance than films	More patient compliance
5	Low dose can only be Incorporated	High dose can be Incorporated
6	It has a fear of chocking	No risk of chocking

Classification of Oral Films[6]

There are three different subtypes of oral films:

1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained-release wafers Types of oral films and their properties are described in Table 2.

Table 2: Types of Oral Films and their Properties.

Sl No	Property/Sub/Type	Flash Release Water	Mucoadhesive Melt-Away Wafer	Mucoadhesive Sustained Release Wafer
1	Area (cm2)	2-8	2-7	2-4
2	Thickness (µm)	20-70	50-500	50-250
3	Structure	Film: single layer	Single or multilayer System	Multi layer system
4	Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
5	Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid Solution
6	Application	Tongue (upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity
7	Dissolution	Maximum 60 sec	Disintegration in a few mins, forming gel	Maximum 8-10 hrs

Formulation of Fast Dissolving Films

Fast dissolving Oral films include various ingredients for its formulation such as

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Superdisintegrants
- Sweetening agent
- Saliva stimulating agent
- Surfactants
- Flavoring agent
- Coloring agent

Formulation of FDFs 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 OS should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms. A typical composition includes various ingredients which are described in the Table 3.

Table 3: A typical composition contains the following ingredients.

Sl No	Agents	Concentration
1	Drug	1-25%
2	Water Soluble Polymer	40-50%
3	Plasticizers	0-20%
4	Fillers, Colours, Flavours Etc.	0-40%

Active Pharmaceutical Ingredient[31]

The film composition contains 1-30% w/w of the active pharmaceutical ingredient. Always use low dose active pharmaceutical ingredients because high dose of drug are difficult to incorporate in fast dissolving film. A number of drugs can be used as fast dissolving oral film including anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, antiemetic, etc.[32] Dimenhydrinate can also be incorporated into ODFs for taste masking. Common examples of drugs incorporated into ODFs are salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc. are mentionedin Table 4.[33]

Table 4: List of few drug that can be incorporated in fast dissolving film.[34,38]

Sl. No.	Drug	Dose	Therapeutic action
1	Azatidine Maleate	1mg	Anti histaminic
2	Nicotine	2mg	Smoking cessation
3	Loperamide	2mg	Anti diarroheal
4	Ondensetron	2.5mg	Anti emetic
5	Triplodine hydrochloride	2.5mg	Anti histaminic
6	Zolmitritpan	2.5mg	Anti migraine
7	Salbutamol	4mg	Anti histaminic
8	Chlorpheniramine Maleate	4mg	Anti allergic
9	Cetrizine	5-10mg	Anti histaminic
10	Acrivastine	8mg	Anti histaminic
11	Loratidine	10mg	Anti histaminic
12	Omiprazole	10-20mg	Proton pump inhibitor
13	Famotidine	10mg	Antacid
14	Ketoprofen	12.5mg	Analgesic
15	Dicyclomine hydrochloride	25mg	Muscle relaxant
16	Diphenhydramine hydrochloride	25mg	Anti allergic
17	Sumatriptan succinate	35-70mg	Anti migraine

Film Forming Polymers

Polymer is the major and most essential component of FDOFs. A variety of polymers are available for preparation of oral film and these are used in the concentration of about 40-45% w/w of total film weight but can be increased up to 65%w/w of film weight alone or in combination to obtain desired properties of oral film.[39] The film obtained should be tough enough so that there may not be any damage while handling or during transportation. The robustness of the film depends on the type of polymer and the amount in the formulation.[40] The physicochemical characteristic of the polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the Prepared film. 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 areglycerol, di-butylpthallate, and polyethylene glycols etc. The commonly used Natural and synthetic polymers are given table 5.

Table 5: List of Some Film Forming Polymers.[41]

Natural polymer	Synthetic polymer
Starch	Hydroxy propyl methyl cellulose
Pectin	Poly vinyl pyrolidone (PVP)
gelatin	Polyvinyl alcohol (PVA)
Sodium alginate	Sodium Carboxy methyl cellulose
Maltodextrin	Poly ethylene oxide (PEO)
Pullulan	Kollicoat IR
Xanthan	Hydroxy propyl cellulose (HPC)
Polymerized rosin	Hydroxy ethyl cellulose (HEC)
Gum acacia	Methyl cellulose (MC)

Ideal Properties Of The Film Forming Polymers.[42,43]

1. The polymer employed should be non-toxic, nonirritant and devoid of any leachable impurities.
2. It should be tasteless.
3. It should have good wetting and spreadability property.
4. The polymer should exhibit sufficient peel, shear and tensile strengths.
5. The polymer should be cheap and readily available.
6. It should have long shelf life.
7. It should not cause any secondary infections in the oral mucosa/ dental region.
8. It should have a good mouth feel property.
9. It would be ideal to have a polymer that would have local enzyme inhibition action.

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-butylpthallate, and polyethylene glycols etc.

Saliva Stimulating Agents.[44]

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 film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. E.g.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 film.

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 polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

Sweetening Agents[45,46]

Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. 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. Low molecular weight carbohydrates and specially sucrose are most commonly used sweeteners. Sucrose is very soluble in water and being colourless does not impart any undesirable colour to the final formulation. It is stable over the pH range 4-8. It mask the taste of both salty and bitter drugs. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The artificial sweeteners have gained more popularity in 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. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200 -300 time sweetness.

Table 6: Comparison of sucrose with saccharin and aspartame.[47]

	Sucrose	Saccharin	Aspartame
Source	Sugar cane, sugar beet	Chemical synthesis; phthalic anhydride, a petroleum product	Methyl ester dipeptide of phenylalanine and aspartic acid
Relative sweetness	1	300	180-200
Bitterness	None	Moderate to strong	none
After taste	none	Moderate to strong; sometimes metallic or bitter	none
Calories	4/g	0	4/g
Acid stability	Good	Excellent	Fair
Heat stability	Good	Excellent	Poor

Flavoring Agents.[48]

Flavoring agents can be selected from the 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. Any flavor can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary flavors such as vanillin, chocolate ,or fruit essence like apple, raspberry, cherry, pineapple. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferred different flavors as per the type and taste of the drugs are mentioned in table 7.

Table 7: Preferred flavors as per the type and taste of the drug.[49]

Drug	Preferred flavor
Antibiotics	Cherry, maple, pineapple, orange, raspberry, banana-vanilla, butterscotch, coconut-custard, fruit-cinnamon, strawberry, vanilla
Antihistamines	Apricot, cherry, cinnamon, grape, honey, lime, peach-orange, peach-rum, raspberry, wild cherry
Barbiturates	Banana-pineapple, banana-vanilla, cinnamon-peppermint, orange, peach-orange, grenadine-strawberry,
Decongestants & Expectorants	Anise, apricot, butterscotch, cherry, coconut-custard, custardmint- strawberry, grenadine-peach, strawberry-lemon, gooseberry, orange-lemon, coriander, pineapple, raspberry.
Electrolyte-solutions geriatrics	Cherry, grape, lemon-lime, raspberry, wild cherry syrup, grenadine-strawberry, lime, port-wine, cherry-wine, wild strawberry. Salt taste drugs Butterscotch, maple Bitter taste drugs Wild cherry, walnut, chocolate-mint, licorice Sweet taste drugs Fruit, berry, vanilla

Colors

A full range of colors is available, including FD&C colors, EU Colors, Natural Colors and custom Pantone matched colors. When drug is present in the film in a suspension or insoluble particulate form, colouring agents have to be incorporated in the oral film. Pigments such as titanium dioxide or FD&C approved colouring agents are generally used (not exceeding concentration levels of 1%w/w).[50-55] 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.

Manufacturing Methods

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

Solvent Casting[56]

Fast dissolving buccal 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.

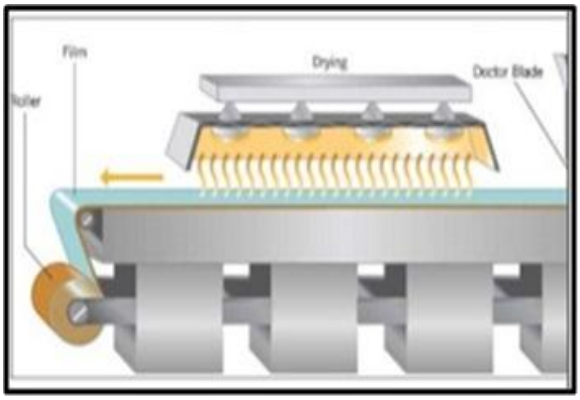


Figure 2: Solvent Casting.

Hot Melt Extrusion.[57]

Hot metal extrusion is commonly used to prepare granules, sustained release tablets, transdermal and transmucosal drug delivery systems. Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971.

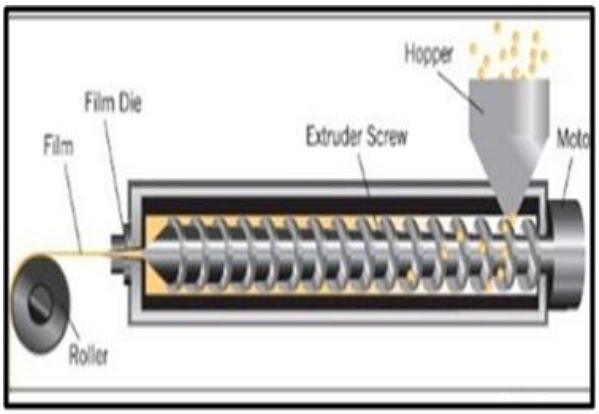


Figure 3: Hot Melt Extraction

Semisolid Casting.[58]

Solution of water soluble film forming polymer is prepared. Resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate). Appropriate amount of plasticizer is added so that gels mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Solid Dispersion Extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70◦ C Finally the solid dispersions are shaped into the films by means of dies.

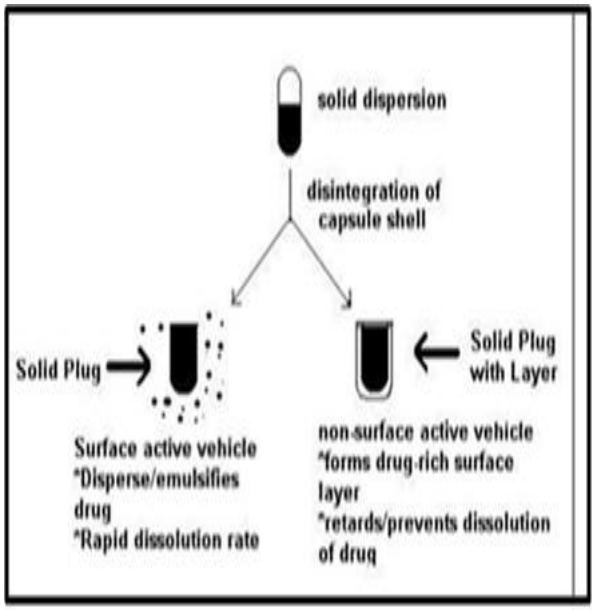


Figure 4: Solid Dispersion Extrusion Method

Rolling Method[59]

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.

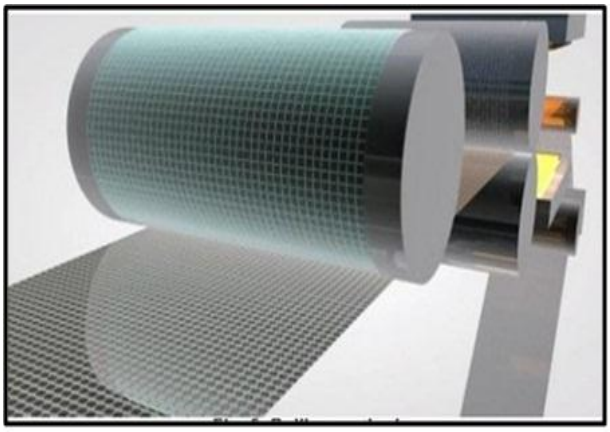


Figure 5: Rolling Method.

Characterization of Fast Dissolving Films[60-66]

Thickness: As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations.

Dryness test/tack tests: 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.

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:

$$\text{Tensile strength} = \frac{\text{Load at Failure X 100}}{\text{Strip thickness X Strip Width}}$$

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 content increases.

-

$$\% \text{ Elongation} = \frac{\text{Increase in length} \times 100}{\text{Original length}}$$

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 as follows:

$$\text{Young's modulus} = \frac{\text{Force at corresponding strain}}{\text{Cross sectional area}} \times \frac{1}{\text{Corresponding strain}}$$

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 51 mm (2 in)/min is employed and is designed 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 specimen is recorded as the tear resistance value in Newton's (or pounds-force).

Weight Variation: Weight variation is studied by individually weighing 10 randomly selected films and by calculating the average weight.

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.

Surface pH of film: The surface pH of fast dissolving film was determined in order to investigate the possibility any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. The pH was measured by bringing the electrode in contact with the surface of the oral film which was previously wet with the help of water.

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 which is then submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weigh was observed. The degree of swelling was calculated using parameters

$$\alpha = (wt - wo)/wo$$

Wt is weight of film at time t, and wo is weight of film at time zero.

Transparency: The transparency of the films can be determined using 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:

Transparency = (logT600)/b = - €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%.

Disintegration time: Disintegration of orally fast dissolving films requires US disintegration apparatus. The disintegration time limit of 30 seconds or less for

orally disintegrating tablet described in Centre for Drug Evaluation and Research (CDER) guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 secs. 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 described in any of the pharmacopoeia. 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.

Stability studies: Stability studies have to be carried out at accelerated condition (65% relative humidity and 35 ºC temperature) in the humidity chamber.

Packaging of Fast Dissolving Film.[67]

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 raid 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 peelable 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 nutriceutical 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 vaccum-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.

Figure 6: Blister Card.

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 Polychloro trifluoro ethylene (PCTFE) film, Polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapour barrier. Lack of clarity is still a drawback.

Application of Fast Dissolving Film.[68]

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of FDFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. Dissolvable FDFs 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.

Topical applications: The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

Gastro retentive dosage systems: Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.

Diagnostic devices: Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

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 drug, generic and brand name from market due to lower cost and consumer preference. This technology is a good tool for product life cycle management for increasing the patent life of existing products. OFDFs are also having great potential of delivering the medicinal agent systemically as well locally and have several advantages over many dosage forms even over the fast disintegrating tablets. This explains the extensive research actively going on this technology. So this technology is growing in fast pace challenging most of the pharmaceutical companies to develop oral films for a wide range of active pharmaceutical ingredients.

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