



Fast Dissolving Films: A Novel Approach to Oral Drug Delivery

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Review Article

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Abstract

In the recent years, many of the pharmaceutical groups are focusing their research on rapid dissolving technology. 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. The main advantage of this technology is the administration to pediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated. This fast dissolving drug delivery system (FDDS) is suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. 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. The present review provides an account of various formulation considerations, method of preparation and quality control of the OFDFs.

Keywords: *Fast dissolving Films, Buccal film, Improved Patient Compliance, Pediatric Patients, Geriatric Patients.*

Introduction

In the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms formulate the fast dissolving tablets by using superdisintegrant/s and hydrophilic ingredients which has the higher bioavailability, quick action and most patient compliance. Many FDTs are prepared by using the expensive lyophilisation process and sometimes difficult to carry, store and handle (fragility and friability).also fear of choking with fast dissolving tablet¹.

To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. Fast dissolving films are very similar to ultra-thin strip of postage stamp in their shape, size and thickness. Fast dissolving films are formulated using polymers, active pharmaceutical ingredients (API), plasticizers, saliva stimulating agents, sweeteners, flavors, preservatives and colors. Fast dissolving film is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at \$500million in 2007 and could reach \$2 billion. More importantly, prescriptions of fast dissolving films have been now approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly.

Special features of Fast Dissolving Films

- Thin elegant film
- Available in various size and shapes
- Unconstructive
- Fast disintegration
- Rapid release



- Have an acceptable taste.
- Give a pleasing mouth feel.
- Should not leave residue in mouth.

Advantages^{4,5,6}

- Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds.
- Fast Dissolving Film is flexible so they are not as fragile and need not any kind of special package for protection during transportation and storage as compared to FDT.
- No need of water has led to better satisfactoriness amongst the dysphasic patients.
- No fear of choking as compared to FDT.
- The large surface area available in the film dosage form allows rapid wet by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and on increase the bioavailability
- The dosage form can be consumed at any place and any time as per convenience of the individual

Disadvantages

- Dose uniformity is a technical challenge
- Hygroscopic in nature
- High doses cannot be incorporated
- Require special packaging for products stability and safety

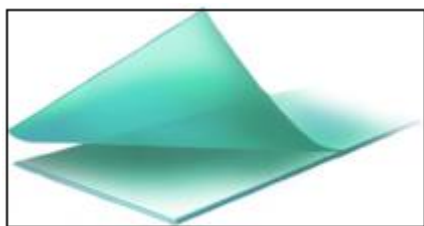


Figure 1: Fast Dissolving Film

Composition of the system

Fast dissolving film is a thin film with an area of 2-8 cm² containing an active ingredient. The immediate dissolution, in water or saliva is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 30mg. Formulation considerations have been reported as important factors affecting mechanical properties of the films. The excipients used in formulation of fast dissolving films are also discussed in detail. From the regulatory perspectives, all excipients used in the formulation should be generally regarded as safe (*i.e.* GRAS listed) and should be approved for use in oral pharmaceutical dosage forms⁷.

Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. Like antiulcers, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal etc. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). Some of the examples of suitable drug molecule that can be incorporated in the FDF.

Tablet 1: Composition of Film Active Pharmaceutical agents⁸

Sr. No	Category	Percentage amount%
1	Drug (API)	1-30%
2	Polymer	40-50%
3	Plasticizer	0-20%
4	Surfactant(Solubility Enhancer)	q.s
5	Saliva stimulating agent	2-6%
6	Sweetening agent	3-6%
7	Flavoring agent	0-10%
8	Coloring agent	q.s
9	Stabilizing agent or Thickening agent	0-5%

The ideal characteristics of a drug to be selected

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose less than 30mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug has stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue

Water soluble polymers^{9,10}

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. The water-soluble polymers achieve rapid disintegration, good 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. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan,



carboxymethylcellulosecekol 30, Polyvinylpyrrolidone PVP K-90, Pectin, Gelatin, Sodium Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGITRD10. Polymerized rosin is a novel film forming polymer.

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-butylphthalate, and polyethylene glycol etc.

Saliva stimulating agent¹¹

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 solubilising 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^{12,13}

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. 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.

Flavoring agents¹⁴

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, sweetmint, 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

Colour

A full range of colors is available, including FD&C colors, EU Colours, Natural Colours and custom Pantone matched colours. 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.

Methods of manufacture of fast dissolving films

One (or a combination) of the following processes may be used to manufacture the oral films:

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

Solvent Casting¹⁵

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.

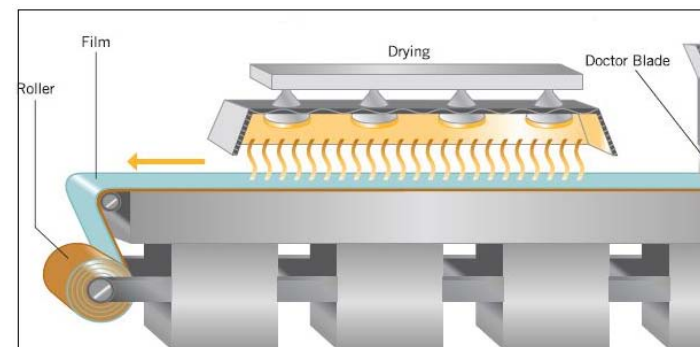


Figure 1: Solvent casting



Hotmelt extrusion¹⁶

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.

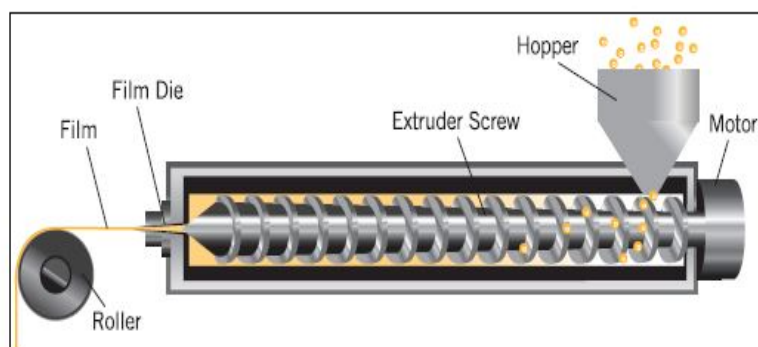


Figure2: Hot melt extrusion

Semisolid casting¹⁷

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.

Rolling method¹⁸

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.

Characterization of fast dissolving films^{19,20,21,22,23}

Drug-excipients interaction studies

Assessment of possible incompatibilities between an

active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (X-RD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction.

Thickness

Thickness test can be carried out using an electronic micrometer. The thickness of the film sample should be measured at five locations (center and four corners), and the mean thickness is calculated. Samples with air bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from analysis.

Folding endurance

To determine folding endurance, a strip of film is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Swelling index

The studies for swelling index of the film are conducted in stimulated salivary fluid. The film sample is weighed and placed in a pre weighed stainless steel wire sieve. The mesh containing the film is submerged into 50 ml of stimulated salivary medium contained in a mortar. Increase in weight of the film is determined at each interval until a constant weight is observed. The degree of swelling is calculated using the formula:

$$SI = \frac{w_t - w_0}{w_0}$$

Where SI is the swelling index,
 w_t is the weight of the film at time "t",
 w_0 is the weight of film at t = 0

Tensile strength

The tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film. Evaluated this mechanical property by using Testing Instrument. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the



calculations. Measurements were run in triplicate for each film. Tensile strength is also defined as the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film from the following equation .

$$\text{Tensile strength (N/mm}^2\text{)} = \frac{\text{breaking force (N)}}{\text{cross sectional area of sample (mm}^2\text{)}}$$

Percent elongation:

The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation can be obtained by following equation:

$$\% \text{ Elongation} = \frac{\text{Increase in length at breaking point(mm)}}{\text{original length(mm)}} \times 100$$

Palatability test:

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade it would be the very good formulation.

Grades: A= very good, B= good, C=poor.

Disintegration test:

Disintegrating time is defined as the time (second) at which a film breaks when brought into the contact with water or saliva. The disintegration time is the time when a film starts to break or disintegrate. Thickness and mass play a role in determining the dissolvable films physical properties. Disintegration test is done by Disintegration apparatus.

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. *In vitro* release studies are carried out in modified USP XXIII apparatus (paddle over disk).

Stability study:

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance

Packaging of fast dissolving film²⁴

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 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 nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.



Figure 3: Blister card

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 vapour barrier. Lack of clarity is still a drawback.

Application of fast dissolving film²⁵

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.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

Not commissioned; externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.