



A REVIEW- NOVEL APPROACHES OF ORALLY FAST DISSOLVING FILM FOR FAST DISSOLVING DRUG DELIVERY

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ABSTRACT

Recently in the market orally fast dissolving films (OFDs) have been introduced, as they provide ease of use and convenience over the other dosage forms such as orally disintegrating tablets. The technology evolved over the past few years from the confection and form of breath strips oral care market and become ideal and novel and in the wide range accepted form by consumers, so orally fast dissolving films are gaining the large no. of pharmaceutical industries in their interest. It is a type of drug delivery when this placed in the oral cavity, disintegrate or dissolved without the intake of water within the few seconds. The postage stamp in their shape, size and thickness are very similar. The drug deliver by the films systemically through intragastric, buccal route of administration or sublingual route and also for the local action. This is the convenient way of dosing medication., not only to the special population groups like pediatric, bedridden patient, geriatric and the mentally ill patients, but for the general and normal population.

KEYWORD: pediatric, bedridden patient, geriatric and the mentally ill patients.

INTRODUCTION

Some patients have difficulty in swallowing or chewing solid dosage forms which risk or fear of choking and thus is a major problem in the use of solid dosage forms. Fast dissolving film (FDF) is a new drug delivery system for oral drug delivery. FDF is used in acute conditions such as pain, emesis, migraine, hypertension, congestive heart failure, asthma etc. FDF has gained popularity due to its availability in various sizes and shapes. These are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without

water, ease of swallowing, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients, absorption is possible through the oral mucosa and may improve bioavailability. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.^[1]

There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

Fast dissolving tablets

Fast dissolving tablets (FDTs) are also known as fast disintegrating/melting tablets, Oro-dispersible tablets,

rapimelts, and porous tablets. The FDTs dissolve or disintegrate within 60 seconds when placed in the mouth without drinking or chewing.^[2] The active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the blood stream. But due to certain disadvantages of fast dissolving tablets like: their physical solid form, sometimes difficult to carry, store and handle, leave unpleasant taste/grittiness in mouth if not formulated properly.^[3] Psychological fear of swallowing, chewing or choking, low pressure moulded tablets fabricated by different manufacturing methods and their expensive packaging cost. Moreover FDTs usually have insufficient mechanical strength, so careful handling is required.^[4]

Fast dissolving oral films

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of drugs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething.^[5,6] Fast

dissolving oral films are based on the technology of the transdermal patch. Films are very similar to postage stamp in their shape, size and thickness.^[7] Sometimes taste masking agents are also added to mask the taste of the active ingredient.

Fast dissolving oral films have advantages like: more stable, durable and quicker than other conventional dosage forms, avoid first pass metabolism^[8], pleasant mouth feel, accurate dosing, rapid onset of action and no need of water with patient compliance. Moreover ease of handling and transportability.^[9]

Salient features of fast dissolving drug delivery system.

Ease of administration for patients who are mentally ill, disabled and uncooperative.

- No need of water to swallow the solid dosage form.
- Quick disintegration and dissolution of the dosage form.
- Drugs absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of the drug is increased.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Overcomes unacceptable taste of the drugs.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.^[10,11]

The concept of oral dissolving film.

This delivery system consists of a thin film

1. After placing it on the top of the tongue, the film dissolves within seconds, avoiding first pass metabolism and may increase the bioavailability of drug.^[12]
2. Accessibility of larger surface area leads to quick disintegration and dissolution in the oral cavity within seconds due to rapid wetting by saliva.^[13]
3. Oral 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 fast dissolving tablets.
4. No need of water has led to better satisfactoriness amongst the dysphasic patients and to better acceptance during travelling without carrying water.

5. No fear of choking as compared to fast dissolving tablets.
6. The large surface area available in the film dosage form allows rapid wettive 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.^[14]
7. The dosage form can be consumed at any place and any time as per convenience of the individual.
8. The first pass effect can be avoided, so a reduction in the dose which can lead to reduction in side effects associated with the molecule.^[15]

Method of preparation of formulation of fast dissolving tablet.

1. Lyophilization or freeze drying

Formation of porous product in freeze-drying process is exploited in formulating FDT. Lyophilization is a process, which includes the removal of solvent from a frozen suspension or solution of drug with structure-forming additives. Freeze-drying of drug along with additives imparts glossy amorphous structure resulting in highly porous and lightweight product. The resulting tablet has rapid disintegration and dissolution when placed on the tongue and the freeze-dried unit dissolves instantly to release the drug. The FDTs formed by lyophilization has low mechanical strength, poor stability at higher temperature, and humidity. Along with above complications and its expensive equipment freeze-drying use is observed to be limited.^[16]

2. Tablet molding

Tablets formed by molding process are highly porous in structure, resulting in high rate of disintegration and dissolution. This process includes moistening, dissolving, or dispersing the drugs with a solvent then molding the moist mixture into tablets by applying lower pressure in compression molding, but always lower than the conventional tablet compression. The powder mixture may be sieved prior to the preparation in order to increase the dissolution. Molded tablets have low mechanical strength, which results in erosion and breakage during handling.^[17]

3. Direct compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the formulation of FDT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.^[17]

4. Spray-drying method

Spray drying is a transformation of feed from a fluid state into a dried particulate form by spraying the feed into a hot drying medium. The main aim of drying is to obtain dry particles with desired properties. Fast dissolving tablets are made up of hydrolyzed or unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulk agent, and sodium starch glycolate or

croscarmellose sodium as disintegrating agent. Sometimes in order to improve the disintegration and dissolution, citric acid and sodium bicarbonate are used. Finally, the formulation is spray-dried in a spray drier. Fast dissolving tablets prepared through this method are disintegrated in less than 20 seconds.^[18]

5. Sublimation

The key to rapid disintegration for fast dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fail to dissolve rapidly because of low porosity of the matrix. Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. The volatile material was then removed by sublimation, leaving behind a porous matrix. In which Mannitol is used as a matrix former, and camphor was used as a sublimating agent. That yields highly porous tablets with satisfactory mechanical strength and a high dissolution rate.^[18]

6. Mass extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets.^[19] The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby making their bitter taste.^[20]

7. Melt granulation

It is a process in which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate®, PEG – 6 – stearate).^[16]

8. Phase transition process

It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making FDTs without any special apparatus. FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.^[20]

Method of preparation of formulation of fast dissolving film.

1. Solvent casting method

In solvent casting method water soluble polymers are dissolved in water 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 dried and cut in to uniform dimensions.^[21]

2. Semisolid casting

In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer, film forming polymer should be 1:4.^[22]

3. Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion method.^[23]

- Fewer operation units.
- Better content uniformity.
- An anhydrous process.

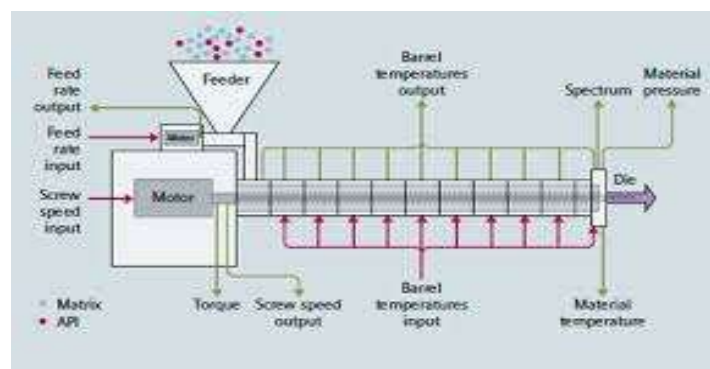


Fig 1- Hot melt extrusion method

4. Solid dispersion extrusion

In this method immiscible components are extruded with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.^[22]

5. Rolling method

In the rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water

and a mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes.^[23] Other ingredients including active agent are dissolved in a small portion of aqueous solvent using a high shear processor. Water-soluble hydrocolloids dissolved in water to form a homogeneous viscous solution.

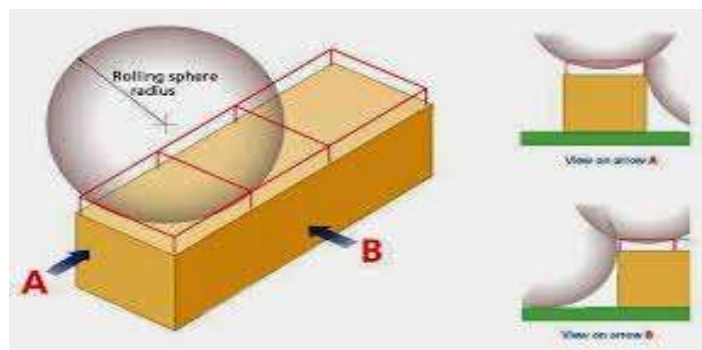


Fig: 2 Rolling method for oral film

Composition of the fast dissolving drug delivery system

Mouth-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.

A mouth-dissolving film has the following components

1. Active Pharmaceutical agents

Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. It includes antiulcers, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal etc. For the effective formulation, dose of drug should be in mg (less than 20 mg/day). Various categories of drugs such as antiemetic, neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorants and antitussive.^[24-31]

The ideal characteristics of a drug to be selected are as follows

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

- Drug requires no water for oral administration for dissolve/disintegrate in mouth in a matter of seconds.
- Have an acceptable taste-masking property.
- Be harder and less fragile.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- The drug should have the ability to permeate oral mucosal tissue.
- Leave minimal or no residue in mouth after administration.
- Allows the manufacture of tablets using conventional processing and packaging equipments.

2. Water-soluble polymers

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 the polymer film bases. Some of the water-soluble polymers used as film formers are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, Carboxymethyl-cellulose-CK 30, Polyvinylpyrrolidone PVP K-90, Pectin, Gelatin, Sodium alginate, Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and Eudragit-RD10. Polymerized rosin is a novel film-forming polymer.^[32,33]

3. Plasticizers

Formulation considerations (Use of plasticizer) 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, dibutylphthalate and polyethylene glycols etc.

4. Saliva Stimulating Agent

More saliva production helps in the faster disintegration of the fast dissolving film formulations. So the formulations should contain acids which are used in the preparation of food 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.^[34]

5. Flavoring agents

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 and pineapple. The amount of flavor needed to mask the taste depends on the flavor type and its strength.^[35]

6. Sweetening agents

Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical sources of sweetener are sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. 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.^[36,37]

7. Coloring agents

FD & C approved coloring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films, eg. Titanium dioxide^[8].

8. Surfactants

Surfactants act as solubilizing or wetting or dispersing agent in formulation so the film gets dissolved within seconds and releases active agent quickly. Some of the commonly used surfactants are sodium lauryl sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent^[39].

Evaluation of fast dissolving film

1. Thickness

As the thickness of film is directly concern with drug content uniformity, 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.^[8]

2. Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below-

$$\text{Tensile Strength} = \frac{\text{Load at breakage}}{\text{Strip thickness} \times \text{strip width}}$$

By using above equation tensile strength of film can be calculated.^[8]

3. 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.^[8]

4. Disintegration time

Disintegration of orally fast dissolving films requires U.S.P. disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in C.D.E.R. 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 seconds. Although, no official guidance is available for oral fast disintegrating films.^[8]

5. In vitro drug release

Dissolution studies of films are performed by U.S.P. XXIII type II apparatus in 6.8 phosphate buffer (500ml) and 0.1N HCl (500ml). The temperature required is 37±0.5°C and the rotation speed should generally 50 rpm. The samples are needed to withdrawn at various time intervals and should analyze spectrophotometrically.^[8]

6. Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film samples into rectangles and placed on the internal side of the spectrophotometer cell. The determine transmittance of films at 600 nm. The transparency of the films was calculated as follows:

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

Where T₆₀₀ is transmittance at 600 nm and b the film thickness (mm) and c is concentration^[38,39].

Application of fast dissolving film

1. 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 topical conditions.

2. 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.

3. 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.

Packaging of orally fast dissolving film

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

The material selected must have the following characteristics:

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

1. 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.



Fig 3 packing of oral film (foil, paper or plastic pouches)

2. 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.

3. Blister card with multiple units

Can be used. It consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.^[40]

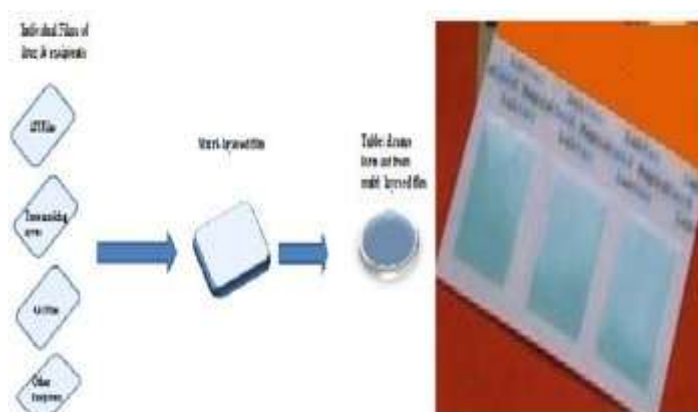


Fig: 4 Blister card for packing of oral film

4. Barrier films

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

CONCLUSION

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

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