



REVIEW ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH
AND BIO-SCIENCE

A Path for Horizing Your Innovative Work

ORALLY FAST DISSOLVING FILMS AS DOMINANT DOSAGE
FORM FOR QUICK RELEASE

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Accepted Date: 31/05/2011

Publish Date: 27/06/2012

Abstract: 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. 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.

INTRODUCTION¹⁻⁷

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical Conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.

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. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment 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). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at \$500 million in 2007 and could reach \$2 billion by 2010. However only a few products consisting bitter molecules have been able to be commercialized because of the complexity associated with the ODT.

Special features of mouth dissolving films⁸

- Thin elegant film
- Available in various size and shapes

- Unconstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release
- The ideal characteristics of a drug to be selected
- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good 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.

Advantage of orodispersible films⁸

- Oral dissolving films can be administered without water, anywhere, any time.
- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
- Suitability for geriatric and pediatric patients, who experience difficulties in

swallowing mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.

- Beneficial in cases such as motion sickness, acute pain, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- As compared liquid formulations, precision in the administered dose is ensured from each strip of the film.
- 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. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.

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| <ul style="list-style-type: none"> • Provide new business opportunity like product differentiation, product promotion, and patent extension. | <p>Disadvantages⁸</p> <ul style="list-style-type: none"> • High doses cannot be incorporated. • Dose uniformity is a technical challenge |
|---|--|

Table 1

Comparison between orally fast dissolving films and oral Disintegrating tablets are given in

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

FORMULATION CONSIDERATION

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

Active pharmaceutical ingredient⁹⁻¹⁴

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 OFDFs. Multivitamins upto 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the OFDFs. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OFDF, the taste needs to be masked.

Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with

pleasurable taste. This is often termed as obscuration technique. The drugs which have incorporated via orally fast dissolving films are mentioned below in Table 2.

Table 2

The drugs which incorporated via orally fast dissolving films are mentioned below

Drug	Action	Dose (mg)
Salbutamol	Anti asthmatic	4
Levocetirizine	Antihistaminic	75
Chlorohexidine	Antiseptic	12
Ondensteron	Anti emetic	2.5

Film forming polymer¹⁵⁻²⁰

Since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity, the final film that is used must necessarily be water soluble. In order to prepare a thin film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very

expensive. Many different polymers for use in oral films are proposed in the literature, and various research groups have introduced different materials.

The polymers can be used alone or in combination to improve hydrophilicity, flexibility, mouth-feel and solubility characteristics of fast dissolving films. The stiffness of the strip depends on the type of polymer and the amount of polymer in the formulation. Polyvinyl pyrrolidone films are brittle in nature and therefore copovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating films. Combination of microcrystalline cellulose and maltodextrin

has been used to formulate fast dissolving films of piroxicam made by hot melt extrusion technique. In this case, microcrystalline cellulose is used to render the film non-sticky and smooth. Microcrystalline cellulose was also used to decrease the disintegration time and improve the dissolution of drug from the films.

Water soluble polymer that may be used include natural gums such as those derived from guar, xanthan, acacia, Arabic or tragacanth, Other available polymers are, polyethylene oxide, acrylic based polymer and several types of sodium carboxymethyl cellulose (CMC), several types of hydroxypropyl methyl cellulose (HPMC), a synthetic copolymer of polyethylene glycol–polyvinyl alcohol (Kollicoat IR) and sodium alginate. Cellulose ethers are widely available and economical. Pullulan, an α -1, 6-linked maltotriose produced from the fungus *Aureobasidium pullulans*, has also been used. Five starches and maltodextrin have also been investigated as alternative film formers. The physicochemical characteristic of the polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the cast thin film oral dosage form.

Plasticizer²¹

Plasticizer is a vital ingredient of the fast dissolving films. Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of film. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that

the use of certain plasticizers may also affect the absorption rate of the drug.

Sweetening agents^{22, 23}

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 % w/w either alone or in combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouthfeel and cooling sensation. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients.

Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness.

Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Aspartame was used for the preparation of oral strips of valdecoxib. Sucralose and neotame was reported to be used in the suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron respectively.

Saliva stimulating agent²⁴

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. 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 strip.

Flavoring agents²⁵

Preferably up to 10% w/w flavors are added in the OFDF formulations. The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 mins.

The selection of flavor is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants

like leaves, fruits and flowers. 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. Flavoring agents for taste masking is given in Table 3.

Table 3

Flavoring agents for taste masking

Basic Taste	Recommended Flavors
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry.
Sour	Citrus flavor, licorice, root beer, raspberry.

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. E.g. Titanium dioxide.

METHOD OF PREPARATION

One or more of the following process can be used combinly to manufacture the mouth dissolving films.

- Solvent casting
- Semisolid casting
- Hot melt extrusion

- Solid dispersion extrusion

- Rolling

Solvent casting method^{26, 27}

In solvent casting method excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.

Semisolid casting^{26, 27}

This method is preferably adopted when acid insoluble polymers are to be used in the

preparation of the films. In Semisolid casting method gel mass is casted in to the films or ribbons using heat controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. Acid-insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

Hot melt extrusion^{28,29}

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. The processing temperatures should be 80⁰C (zone 1), 115⁰C (zone 2), 100⁰C (zone 3) and 65⁰C (zone 4). The extrudate (T = 65⁰C) then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion.

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

Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions

are prepared. Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method²⁸

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes.

EVALUATION PARAMETERS²⁹⁻³¹

Morphology study

The morphology of the films is studies using electron microscopic (SEM), at definite magnification.

Weight Variations

Weight variation is studies by individually weighing 10 randomly selected films and calculating the average weight. The average weight should not deviate significantly from the average weight.

Thickness

The thickness of film is determined by screw gauge or micrometer at different points of the films.

Drug content

A film of size 2 cm² was cut and put 10 ml of volumetric flask which containing solvent. This was then shaken in a mechanical shaker for 2 hrs to get a homogeneous solution and filtered. The drug was determined spectroscopically by appropriate dilution.

Tensile strength

Tensile strength of films was determined using an apparatus fabricated in laboratory. A small film strip (2 cm²) was cut and fixed to assembly. The weight required to break the film was noted and simultaneously film elongation was measured with the help of pointer mounted on the assembly.

$$\text{Tensile strength} = \frac{\text{break force}}{ab} (1 + \frac{\Delta L}{L})$$

a, b and L are width, thickness, and length of the strip, and ΔL is the elongation at break.

Percentage elongation

Determined by noting the distance travelled by pointer before break of the film on the graph paper.

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

Folding endurance

Folding endurance is evaluation of films involves determining the folding capacity of the films when subjected to frequent extreme condition of folding. It was

determined by repeatedly folding the film at same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave value of folding endurance.

Disintegration test

Determined manually by dipping the film in 10 ml of water in beaker with gently shaking when film was dissolved, time was noted.

***In vitro* drug release**

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 study was carried out for all the batches at accelerated condition 65% relative humidity and 35 °C (temperature) in the humidity chamber for the three months. After 3 months the films were evaluated for the drug content, disintegration time and physical appearance observation.

Packaging³³

A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films. Which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. 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.

Commercial Marketed Fast Dissolving Oral Film is given in Table 4.

Table 4

Commercial Marketed Fast Dissolving Oral Film.

Product	Manufacturer	Active Pharmaceutical Agent	Strength (mg)
Triaminic	Novartis	Dextromethorphan HBr	7.5
Triaminic	Novartis	Diphenhydramine HCl	12.5
Theraflu	Novartis	Dextromethorphan HBr	15
Gas-X	Novartis	Simethicone	62.5
Sudafed	Pfizer	Phenylephrine HCl	10
Benadryl	Pfizer	Diphenhydramine HCl	12.5
Chloraseptic	Prestige	Benzocaine Menthol	3/3
Suppress	InnoZen	Menthol	2.5
Orajel	Del	Menthol/Pectin	2/30
Listerine	Pfizer	Cool mint	-

CONCLUSION

OFDFs are not well defined in the literature but, no doubt a revolutionary and an innovative drug delivery system for all the population groups, specifically geriatric, pediatric patients and patients with swallowing difficulties. 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.

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