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A NOVEL APPROACH IN ORAL FAST DISSOLVING DRUG DELIVERY SYSTEM – A REVIEW

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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.

Key words: Fast dissolving Films, Buccal film, Improved Patient Compliance, Pediatric Patients, Geriatric Patients.

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INTRODUCTION:

The oral route of drug administration is the most important method of administration of drug for systemic effect, despite of tremendous advancement in drug delivery system. Its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose. Mouth dissolve products (tablets and films) may show greater patient acceptability and convenience. Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing[1-2]. After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, Fast-dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. FDFs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething[3-5]. Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolve/disintegrate in the mouth within few seconds without water and eliminates the fear of chocking as an alternative to fast dissolving tablets. Basically the fast dissolving film can be considered as an ultra thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. Most fast dissolving films are having taste masked active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipients.

The advantages of convenience of dosing and portability of mouth dissolving film have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally. Because of fast dissolving behavior and fast adherence to the mucosa, fast dissolving films cannot be spit after application on to the tongue. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery

system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half life and bioavailability enhancement of drugs.

Formulation of fast dissolving film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents. From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms. Fast dissolving films evolved over the past few years from the confection and oral care market in the form by consumers for delivering vitamins and personal care products.

Special features of Fast Dissolving films[6-7]

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release

Advantages[8-9]

- Convenient dosing
- No water needed
- Taste masking
- No risk of chocking
- Enhanced stability
- Improved patient compliance
- Rapid disintegrating and dissolution in the oral cavity
- Flexible and portable nature provides ease in transportation, handling, storage
- Avoids first past metabolism

Disadvantages[10]

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

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 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.

COMPOSITION OF THE SYSTEM

Fast dissolving film is a thin film with an area of 2-8 cm^2 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[11]**.** Formulation considerations have been reported as important factors affecting mechanical properties of the films. From the regulatory perspectives, all excipients used in the formulation should be generally regarded as safe (i.e. GRAS-listed).

A typical composition contains:

Active pharmaceutical agents	1-25%
Water soluble film forming polymer	40-50%
Plasticizers	0-20%
Sweetening agent	3-6%
Saliva stimulating agent	2-6%
Colors, flavors etc	0-10%

Table 1: List of drug molecule that can be incorporated in the oral strip

DRUG	DOSE	THERAPEUTIC CLASS
Chlorpheniramine maleate	4 mg	Anti allergic
Triplolidine hydrochloride	2.5 mg	Anti histaminic
Loperamide	2 mg	Anti diarroheal
Famotidine	10 mg	Antacid
Azatidine maleate	1 mg	Anti histaminic
Sumatriptan succinate	35-70 mg	Anti migraine
Ketoprofen	12.5 mg	Analgesic
Nicotine	2 mg	Smoking cessation
Psuedoephedrine hydrochloride	30 mg	Bronchodilator
Acrivastine	8 mg	Anti histaminic
Loratidine	10mg	Anti histaminic

Active Pharmaceutical agents[12]

Active pharmaceutical substance can be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa. Like antiulcers, antiasthma tics, 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 OS are listed in following Table 1.

Film forming Polymers[13-14]

A variety of polymers are available for preparation of fast dissolving films. 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. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation. The various polymers which can be used for making fast dissolving films must be water soluble with low molecular weight and excellent film forming capacity, since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity. The polymer employed should be non-toxic, non-irritant with good wetting and spreadability property. The polymer should not be very expensive and should be readily available. Water soluble polymer that may be used include natural gums such as xanthan, guar, acacia, tragacanth other available polymers include cellulose or cellulose derivatives, hydroxypropylmethyl cellulose with different grades like HPMC E15, HPMC E5, HPMC K4M, HPMC K100, hydroxyethylcellulose, hydroxypropylcelluose, carboxymethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, pullulan, gelatin. Modified starches are also used for preparation. 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.

Plasticizer

Plasticizer is a vital ingredient of fast dissolving films. The mechanical properties such as tensile strength and elongation to the films can be improved. It also helps to improve the flexibility of the strip and reduces the brittleness of the film. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. The flow of polymer also gets better by addition of the plasticizer[15-16]. The selection of the plasticizer will depend upon its compatibility with the polymer and also the type of the solvent employed in its casting of the

film. Inappropriate use of the plasticizer may lead to film cracking, splitting, peeling and it may also affect the absorption rate of the drug. The commonly used plasticizers are glycerol, sorbitol, propylene glycol, low molecular weight polyethylene glycols, citrate derivatives, castor oil etc.[17]

Sweetening agents

Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Sweeteners can be used either alone or in combination. Both natural as well as artificial sweeteners are used in the formulation of these fast dissolving films. But the use of natural sugars in such preparations needs 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 pharmaceutical preparations. 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. 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[18].

Saliva stimulating agents

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in faster disintegration of the fast dissolving film. These agents can be used either alone or in combination. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Commonly used saliva stimulating agents are citric acid, lactic acid, ascorbic acid, malic acid, tartaric acid[19].

Flavoring agents

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, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors[20]. Apple, raspberry, cherry,

pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

Coloring agents

A full range of colors is available including FD& C colors, EU colors, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc dioxide and custom pantone-matched colors. These all coloring agents should not exceed Concentration levels of 1% w/w. these agents are incorporated when some of the formulation ingredients or drugs are present in insoluble or suspension form.

METHOD OF PREPARATION OF FAST DISSOLVING FILM[21-23]

One or a combination of the following processes can be used to manufacture the Mouth dissolving film:

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

1. Solvent casting method

Fast dissolving 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.

Water soluble ingredients are dissolved in water and

API and other agents are dissolved in suitable solvent to form a clear viscous solution

↓

Both the solutions are mixed

↓

Degassed under vacuum

↓

Resulting solution is cast as a film

↓

Film is dried in drying oven and collected

2. Hot melt extrusion

Hot melt extrusion method has various benefits; those are fewer operation units, minimum product wastage, better content uniformity, an anhydrous process, absence of organic solvents.

In hot melt extrusion method-

Drug is mixed with carriers in solid form.

↓

The extruder having heaters melts the mixture

↓

Finally the melt is shaped in films by the dies.

3. Semisolid casting method

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. 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.

Solution of water soluble film forming polymer is prepared

↓

Resulting solution is added to a solution of acid insoluble polymer

↓

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.

4. Solid dispersion extrusion method

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 melt of polyethylene glycol, obtainable below $70^{o}C$

↓

Finally the solid dispersions are shaped into the films by means of dies

Precautions while preparing solid dispersions: the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol and polymeric form of drug precipitated in the solid dispersions may get affected by the liquid solvent used.

5. Rolling method

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

PACKAGING

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 (Figure 1)[24].

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

Figure 1: Rapid card

Foil, paper or plastic pouches: The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

Single pouch and aluminum pouch: Soluble film drug delivery pouch is a peel able pouch for "quick dissolve" soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

Blister card with multiple units 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[25]**.**

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.

EVALUATION

- Mechanical properties
  - Thickness
  - Dryness/tack test
  - Tensile strength
  - Young's modulus
  - Tear resistance
  - Folding endurance
- Organoleptic test
- Surface pH test
- Swelling test
- Transparency
- Assay/content uniformity
- Disintegration test
- In-vitro dissolution test

Thickness

The thickness of film is determined by screw gauge or micrometer at different points of the films. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

Dryness/Tack test

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), dry-to-touch, dry-hard, dry through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films, most of the studies can be adapted intricately to evaluate pharmaceutical orally fast dissolving film. 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 available for this study[26].

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks[27]. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below

$$\text{Tensile strength} = \text{Load at breakage} / \text{Strip thickness} \times \text{Strip Width}$$

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[28].

% Elongation = Increase in length ×100 / 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.

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 51mm (2 in)/min is employed and is designed to measure the 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)[29].

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[30-31].

Organoleptic evaluation

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatus methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations[32-33].

Morphology Studies: Scanning electron microscopy (SEM) study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API.

Near-infrared chemical imaging (NIR-CI) study helps in determining the difference between drug distributions in drug loaded films and recrystallization[34].

Surface pH of film : Surface pH of films is determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the color of pH paper was observed and reported.

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. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed[35].

The degree of swelling was calculated using parameters

$$S.I = Wt - Wo/Wo$$

Where S.I is the swelling index, W_t is the weight of the film at time't', and W_o is the weight of film at t = 0.

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:

Transparency = (logT600)/b = - €c

Where T600 is transmittance at 600 nm and b the film thickness (mm) and c is concentration[36-37.]

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 percent.

Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s[38].

Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus. 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[39].

Table 2: FDA approved Fast Dissolving Buccal Films[40-41]

Drug	Year	Use	Company
Suboxone® (Buprenorphine and Naloxone	31/08/2010	Sublingual film indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.	Reckitt Benckiser Pharmaceuticals Inc
Zuplenz	Jan 2010	Prevention of postoperative, highly an Moderately emetogenic cancer chemo therapy and radiotherapy induced nausea and vomiting	PharmFilm® technology
Ondansetron	23rd March 2010	Prevention and treatment of Chemo therapy and Radiotherapy induced nausea, vomiting ("CINV") in adults as well as children aged equal or above 6 months and the prevention and treatment of Post Operative Nausea and Vomiting (PONV) in adults and children aged equal or above 4 years.	APR Applied Pharma Research s.a("APR") and Labtec GmbH("Labtec")
Zelapar	October 2005	Treatment for Parkinson's disease.	Valeant Pharmaceuticals International Inc

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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