



FAST DISSOLVING ORAL FILM FOR FAST DISSOLVING DRUG DELIVERY SYSTEM

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ABSTRACT

Buccal drug delivery has lately become an important route of drug administration. But many of the patients (pediatric and geriatric) are unwilling to take solid preparations due to fear of choking. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Fast dissolving oral drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer, better patient compliance, rapid drug absorption and sudden -onset of drug action with instant bioavailability is possible. So, now-a-days, most of the pharmaceutical companies adopted various technologies to manufacture fast dissolving oral films in large scale despite of several

limitations as an alternative to traditional over-the-counter medicine forms such as tablets, capsules etc. This review reflects information regarding formulation ingredients, technologies and evaluation tests employed in the preparation of fast dissolving oral films.

KEYWORDS: Fast dissolving film, Fast drug delivery system, Mouth dissolving film.

INTRODUCTION

Among the different routes, the most agreeable route for the patients is oral route. Most of the pharmaceutical companies have directed their research activity in developing viable dosage alternatives from oral route for pediatrics, geriatric, noncompliant or nauseous patients. Research in the oral drug delivery segment has led to evolution of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet

to wafer to the recent development of fast dissolving oralfilms.^[1]

Fast dissolving oral film, a novel drug delivery system for the oral delivery of the drugs is an ultra-thin film prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity. It is an ultrathin strip (50- 150 microns thick) of postage stamp size with an active agent and other excipients developed on the basis of transdermal patch technology. These evolved from the confectionery and oral care markets over past decade in the form of breath strips and became a novel and widely accepted dosage form by consumers for delivering vitamins and personal care products. These fast dissolving oral films have persistent to extend in sales and launched as patient compliant and convenient products effectively addressing issues for pharmaceuticals as well as nutraceuticals that have been traditionally administered as oral solid dosages. The delivery system consists of a very thin oral strip, which 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 application². It then rapidly disintegrates in a matter of seconds and dissolves to release medication for oromucosal absorption. Today, fast dissolving oral films are a well proven and worldwide accepted technology for the systemic delivery of active pharmaceutical ingredients (APIs).

ADVANTAGES

Fast dissolving oral films being an advanced evolution of fast dissolving drug delivery systems have some outstanding advantages over conventional dosage forms and orally disintegrating tablets. They are:

- Improved patient compliance.
- As fast dissolving thin oral films are flexible, they are easy to carry, store and handle, which is not the case with orally disintegrating tablets (fragile and brittle).
- Precision in the administered dose is ensured from each of the strips as compared to drops or syrup formulations.
- Water is not needed for administering, so problem encountered in swallowing of tablets or capsules can be avoided.
- Patients suffering from repeated emesis, dysphagia, motion sickness prefer this dosage form as they are unable to swallow large quantity of water.
- Availability of larger surface area leads to fast disintegration and dissolution in the oral cavity.
- As the oral mucosa is being highly vascularized, drugs directly enter the systemic

circulation without undergoing first-pass hepatic metabolism. This results in improved oral bioavailability of molecules.

- These films can be manufactured through economically feasible non-sophisticated procedures and uncomplicated equipment.

DISADVANTAGE

- High dose cannot be incorporated into the film^[3,4]

FORMULATION INGREDIENTS

Drug (1-25%)

Several class of drugs can be formulated as mouth dissolving films including antiasthmatics (Salbutamol sulphate), antiulcer (Omeprazole), expectorants, antitussives, NSAID'S (Valdecoxib, Meloxicam).^[5,6,7]

Water Soluble Polymers (40-50%)

To obtain the desired film properties, polymers can be used alone or in combination.

Generally water-soluble polymers are used as film formers as they achieve rapid disintegration, good mouthfeel and mechanical properties to the films. The strength of the film depends on the type of polymer and the amount in the formulation. By increasing the molecular weight of polymer film bases, disintegration rate of the polymer decreases. Polymers frequently used as film formers are water soluble grades of cellulose ethers, polyvinyl alcohol, polysaccharides, polyvinylpyrrolidone K- 90, polyethylene glycols, pullulan, gelatin, carboxmethylcellulose cekol 30, hydroxy propyl methyl cellulose E-3 and K-3, methyl cellulose A- 3, A-6 and A-15, pectin, sodiungalinate,

Hydroxypropylcellulose, maltodextrins and eudragit RD10 8,9,10.

Plasticizers (0-20%)

Plasticizer enhances mechanical properties such as tensile strength and elongation to the film by reducing the glass transition temperature of the polymer. It also reduces brittleness of the strip as a result improves its flexibility. Choice of plasticizer depends upon type of solvent used and its compatibility with the polymer. Some of the commonly employed plasticizers are phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate,

triacetin and glycerol. Improper use of plasticizer may lead to blooming, film cracking, splitting and peeling of the strip.^[8,11,12,13]

Surfactants

Surfactants are used as wetting or solubilising or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed are poloxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is poloxamer 407.^[14]

Sweetening agents

Some of the commonly employed sweeteners are dextrose, sucrose, fructose, glucose, isomaltose, polyhydric alcohols (sorbitol, mannitol), etc. Artificial sweeteners like saccharin, cyclamate, aspartame (first generation) and acesulfame-K, sucralose, alitame, neotame (second generation) can also be used.^[15]

Saliva stimulating agents

Saliva stimulating agents are used to increase the rate of production of saliva that would help in the faster disintegration of the rapid dissolving strip formulations. Examples of salivary stimulants are citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. Among these the most preferred one is citric acid.^[16]

Flavouring agents

The quantity of flavouring agent required to mask the taste depends on the flavour type and its strength. Commonly employed are fruity flavours (vanilla, cocoa, coffee, chocolate, citrus), flavour oils (peppermint oil, cinnamon oil, oil of nutmeg). Flavours can also be chosen from oleo resins, synthetic flavour oils and extract derived from various parts of the plants like fruits, flowers etc.

Colouring agents

Generally incorporated colouring agents are FD&C colours, natural colours, pigments such as titanium dioxide etc.^[17]

MANUFACTURING METHODS

To manufacture fast dissolving oral films, following methods are generally employed:

- a. Semisolid casting.
- b. Rolling.

- c. Solventcasting.
- d. Solid dispersionextrusion.
- e. Hot meltextrusion.

a. Semisolid casting

In this method at first a solution of watersoluble film forming polymer is prepared. Then the resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate) which was prepared in ammonium or sodium hydroxide. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. A gel mass is obtained on addition of suitable amount of plasticizer. By the means of heat controlled drums, finally the gel mass is casted in to the films or ribbons.^[18]

b. Rolling

Solvents mainly used in this method are water and mixture of water and alcohol. By the means of high shear processor, active agent and other ingredients are dissolved in small portion of aqueous solvent. Water soluble hydrocolloids are dissolved in water to form homogenous viscous solution. Then the resultant solution or suspension containing drug is rolled on a carrier. Finally the obtained film is cut in to desired shapes and sizes.^[19]

c. Solventcasting

In this method water soluble polymers are dissolved in water and the drug along with other ingredients is dissolved in suitable solvent. Then boththe solutions are mixed, stirred, finally casted in to the petri plate and dried.^[18]

d. Solid dispersionextrusion

Firstly solid dispersion is prepared by extruding immiscible components with drug and then shaped in to films by the means of dies.^[19]

e. Hot meltextrusion

In hot melt extrusion method at first drug is mixed with carriers in solid form. Then the mixture is molten by the means of extruder having heaters. Lastly the melt is shaped in to films by the dies.^[20]

TECHNOLOGIES

1) **SOLULEAVES™** technology is used to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. SOLULEAVES™ films can be designed to dissolve rapidly on contact with saliva, quickly releasing the active ingredients and flavours. This quality makes edible films an excellent delivery method for a large range of products requiring fast release in the mouth. For pharmaceutical uses this method of administration is especially useful for pediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. SOLULEAVES™ films can also be designed to adhere to mucous membranes and to release the active ingredient slowly over 15 minutes.

2) **WAFERTAB™** is a drug delivery system that incorporates pharmaceutical actives into an ingestible filmstrip. The system provides rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth.

The WAFERTAB™ filmstrip can be flavoured for additionally improved taste masking. The active ingredient is precisely dosed and integrated into the body of a pre-manufactured XGEL™ film, thus preventing exposure to unnecessary heat and moisture and potentially enhancing product stability. The WAFERTAB™ system lends itself to many possibilities for innovative product design, enabling multiple films with different actives to be bonded together. WAFERTAB™ can be prepared in a variety of shapes and sizes and is an ideal method for delivery of medicines, which require fast release or for use by patients who have difficulty swallowing.

3) **FOAMBURST™** is a special variant of the SOLULEAVES™ technology where an inert gas is passed into the film during production. This results in a film with a honeycombed structure, which dissolves rapidly giving a novel mouth sensation. FOAMBURST™ has attracted interest from food and confectionary manufacturers as a means of carrying and releasing flavours.

4) **XGEL™** film is at the heart of Meldex International's intellectual property used in all its film systems and its ingestible dosage delivery technologies. XGEL™ film provides unique product benefits for healthcare and pharmaceutical products: it is non- animal-derived, approved on religious grounds and is suitable for vegetarians; the film is GMO free and continuous production processing provides an economic and competitive manufacturing

platform. XGEL™ film can be taste masked, coloured, layered, and capable of being enteric properties whilst also having the ability to incorporate active pharmaceutical ingredients. The XGEL™ film systems can be made to encapsulate any oral dosage form, and can be soluble in either cold or hot water. XGEL™ film is comprised of a range of different water-soluble polymers, specifically optimised for the intended use.

All of the XGEL ingredients are well known and generally regarded as safe (GRAS).

EVALUATION TESTS

The fast disintegrating oral films are evaluated for the following parameters

- Thickness of the film
- Disintegration time
- Dissolution time
- Folding endurance
- pH
- Percentage of moisture uptake
- Percentage of moisture content
- Tensile strength of the film
- Surface roughness
- Morphology study
- Swelling property
- Tack test/ Dryness test
- Percent elongation
- Young's modulus
- Transparency
- Contact angle
- Linear expansion coefficient in water

Thickness measurement

Thickness of the film is measured by using a dial gauge tester. Thickness at different points is measured from which the average thickness of the FDOF is determined (Gavaskar et al., 2010).

Disintegration time

It is the time at which the film begins to break when brought into contact with water. It can be determined by keeping a film of desired size in a Petri dish containing water and noting the time it takes to break.

Dissolution time

It is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media. It can be done by both *in vitro* and *in vivo* methods. *In vitro* dissolution time can be determined by keeping a desired piece of film in Petri dish containing water and noting the time required to dissolve at least 80% of the film. *In vivo* dissolving time of film is studied by selecting different aged group of volunteer. The films of desired size should be kept in their oral cavity till they completely dissolve without any residue left in mouth and *in vivo* dissolving time of film is noted (Vishwakarma et al., 2011).

Measurement of folding endurance

In order to carry out the endurance study, the strip of film is repeatedly folded at the same place until it breaks. The number of time the film is folded at the same place prior to breaking gives the folding endurance (Khurana et al., 2000).

pH

pH measurement is carried out by keeping the film in contact with distilled water, and after 1 hour, the pH of the solution or dispersion is measured (Khurana et al., 2000).

Moisture uptake

The test is done by keeping previously weighed film in desiccators at a particular temperature and relative humidity. After three days, the film is taken out and reweighed to determine the percentage of moisture uptake. Percentage of moisture uptake can be calculated as follows, (Saxena et al., 2006).

$$\text{Percentage of moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture content

Previously weighed films are stored in a desiccator for 24 hours. The final weight is noted when there is no further change in the weight of individual film (Saxena et al. 2006). Percentage of moisture content, can be calculated as follows,

$$\text{Percentage of moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Initial weight

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile strength of the film is determined by using tensile testing machine like Instron or Monsanto tester. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below.

Tensile strength =

$$\frac{\text{Load Failure} \times 100}{\text{Strip thickness} \times \text{Strip Width}}$$

Surface roughness

The surface roughness of the film is determined by the using a Profilimeter. Other parameters like elongation, Young's Modulation, bending length and tear resistance of the film can be studied.

Morphology Study

The morphology of the film is studied using scanning electron microscopy (SEM) at a definite magnification. (Mashru et al., 2005).

Swelling Property

Film swelling studies are conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15 ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed (Peh et al., 1999).

Degree of swelling property is calculated by following formula,

$$\text{Swelling Index (SI)} = (W_t - W_0) / W_0$$

Where W_t is the weight of the film at time t and W_0 = weight of the film at $t = 0$.

Tack test/ Dryness 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. All these tests are primarily used for paint films. Tack is the tenacity with

which the strip adheres to an accessory that has been pressed into contact with the strip (Gavaskar et al., 2010).

Percent elongation

On application of stress, 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 with the increasing concentration of plasticizer (Dhire et al., 2011).

Percentage of Elongation =

$$\frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

Young's Modulus

Elastic modulus or Young's modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows: (Rathi et al., 2011).

Young's Modulus =

$$\frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{Cross head speed}}$$

Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. The film samples are cut into rectangles and placed on the internal side of the spectrophotometer cell. This determines transmittance of films at 600nm (Bhyan et al., 2011). The transparency of the film is calculated as:

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

Where T_{600} is the transmittance at 600 nm, b is the film thickness (mm) and c is concentration.

Contact Angle

Contact angle measurements are performed at room temperature with a goniometer (AB Lorentz and Wettre, Germany). A drop of distilled water is placed on the surface of the dry film. Images of the water droplets are recorded within 10 seconds of the deposition by digital camera. The digital pictures are analyzed for contact angle determination using image software (Rathi et al., 2011).

Linear Expansion Coefficient in Water

Film is immersed in water. Specimen is taken at 2,4,6,8,10,15,30 and 60 seconds and the size of the side length is measured. It is calculated as (Siddiqui et al., 2011):

$$L\% = \frac{L_1 - L_0}{L_0} \times 100$$

L_0

Where

L_1 = side length after immersion

L_0 = side length before immersion

Packaging

A variety of options in packaging are available for fast disintegrating oral films. Single packaging is mandatory for films which are pharmaceutical products; an aluminium pouch is the most commonly used packaging system. APR-Labtec has developed the rapid card, a proprietary and patented innovative packaging system which is specifically designed for the rapid films. The rapid card is exactly the same size as a credit card and holds three rapid 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 (Vollmer et al., 2006). Another packing system Core-Peel® is developed by Amcor Flexibles and is gaining popularity in the field of packaging of fast disintegrating oral films.

CONCLUSION

The growing success and popularity of fast dissolving oral film recently in global market is evidence to the need for effective taste masked, "without water" pharmaceutical formulations. Fast dissolving oral films being a natural evolution of fast dissolving drug delivery systems have prominent advantages over conventional dosage forms and orally disintegrating tablets. Due to their immense importance during the emergency cases such as allergic reactions and high patient compliance, fast dissolving oral films have evolved as consumer friendly dosage forms. So many of the pharmaceutical companies are launching this technology as these films can be manufactured through non-sophisticated, uncomplicated equipment and procedures. Due to these, fast dissolving films have economically feasible developmental futuristic opportunities.

Some of the examples of marketed Fast Dissolving Oral Films.

Product	Manufactured by	Indication
Caffeine films	Dow chemical company	CNS stimulant.
Dextromethorphan fast dissolving films	Hughes medical corporation	Anti-tussive agent.
OndansetronRapidfilms®	Labtec Pharma	Postoperative nausea and vomiting.
Methylcobalamin fast Dissolving films	Hughes medical corporation	Peripheral neuropathy, Diabetic neuropathy.
Chloraseptic®Relief strips™	Innozen Inc	Minor irritation, pain and sore throat.
Folic acid fastDissolving films	Huges Medical Corporation	Anemia.
TriaminicThin Strips®	Novartis Pharmaceuticals	Nasal decongestant.
DiphenhydramineHydrochloride films	MonoSolRX	Antihistaminic.

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