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**FAST DISSOLVING ORAL FILMS: AN EMERGING TECHNOLOGY IN DRUG
DELIVERY SYSTEMS**

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ABSTRACT

Fast-dissolving oral films have emerged as alternative dosage forms for the patients who experience difficulties in swallowing traditional oral solid dosage forms such as children and the elderly, but also to the general population. These are solid dosage forms, which disintegrate and dissolve immediately within 1 min when placed in the mouth without drinking water or mastication. This technology has been used for local action as well as rapid release products, to enhance drug bioavailability and also to mask the bitter taste of the drug. These formulations are suitable for cough, cold, sore throat, allergenic conditions, nausea, pain, hypertension and CNS disorders, epilepsy and many more diseases. This review reflects information regarding formulation consideration, manufacturing methods and evaluation tests employed in the preparation of fast dissolving oral films.

KEYWORDS

Fast Dissolving Oral films, Without water, Children, Elderly, Rapid release and Polymers.

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INTRODUCTION

Oral administration is the most preferred route among all other routes. Most of the drugs are taken orally in the form of tablets, capsules, etc. by all patients including adult, pediatric and geriatric patients. The oral route is sometimes problematic because of the swallowing difficulty for pediatric, geriatric and dysphasic patients who have fear of choking. To beat the issues of conventional tablets, a new drug delivery system for the oral delivery of the drugs, was investigated which is known as Fast dissolving films/oral dispersible

film/mouth dissolving films. They disintegrate and dissolve quickly in the oral cavity without the administration of water^{1,2}.

Orally fast-dissolving film is an innovative technology for the oral delivery of the drugs. The delivery system consists of a very thin oral film, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and dissolves at the site of application. FDF is prepared using hydrophilic polymer that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via buccal mucosa^{1,2}.

Salient Features

- Thin and elegant film
- Available in various size and shape
- No risk of choking
- Ease of administration for patients
- Fast disintegration or dissolution
- Rapid release
- Leaves minimal or no residue in the mouth³

Advantages

- Improved oral absorption
- Improved bioavailability
- Improved patient compliance, especially for pediatric and geriatric population
- It is useful in cases where a rapid onset of action is required
- The higher surface area available in the oral cavity leads to faster disintegration and dissolution of the strip
- Thin Films have greater stability
- Drugs bypass the first pass metabolism unlike in the case of conventional dosage forms
- Easily handled, storage and transportation
- Oral films are more flexible, convenient and are not brittle as ODTs
- Pain-free self-administration is possible^[4]

Disadvantages

- Drugs that are unstable at the buccal pH or irritate the mouth mucosa cannot be formulated into thin films

- The films are hygroscopic and may lose its stability in environments having high RH
- It takes a day for the films to dry at room temperature thereby reducing the production rate
- Dose uniformity is a technical challenge
- Expensive packaging of oral film^{3,4}

Benefits of Fast Dissolving Oral Film over Fast Disintegrating Tablets

1. Provide a larger effective surface area for the disintegration.
2. No friability loss
3. Require less expensive processing and packaging materials
4. No fear of choking
5. Requires less excipients
6. Less time consuming process.
7. More elegant
8. More economical⁵⁻⁷

Formulation Consideration

All the excipients used in the formulation and development of oral films must be safe and should be approved. Fast dissolving Oral films include various ingredients for its formulation such as

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Saliva stimulating agent
- Surfactants
- Sweetening agent
- Flavoring agent
- Coloring agent
- Stabilizing and thickening agents^{5,7}

ACTIVE PHARMACEUTICAL INGREDIENT

The ideal characteristics of an API to be selected in FDF

- Taste of API - pleasant.
- The API dose - up to 40 mg.
- The molecular weight of API preferably smaller.
- API should be stable in the fluid present in mouth.

- API should be moderately unionized in oral cavity fluid.
- Permeability through mucosal tissue⁸.

Polymers

The selection of polymers plays an important role in the successful formulation of Oral Dissolving Films, for the preparation of ODF they can be either used alone or in combination with other polymers. Generally 45% is the optimal concentration of the polymer for the preparation of FDF. Hydrophilic polymers are used in the preparation so that film can dissolve rapidly in the oral cavity and drug is delivered to the systemic circulation via dissolution when it comes in contact with the saliva in the buccal cavity. The commonly used polymers are HPMC K5, CMC, PVP K90, HPC, pectin, sodium alginate, polysaccharides, polyethylene glycols, methyl cellulose, and maltodextrins. HPMC is proved to be a better polymer than others^{8,9}.

Ideal Properties of Film Forming Polymers

The polymers should be inert, nontoxic and non-irritant.

The polymer should have a better mouth feel property and good shelf-life.

The polymer should exhibit good spreadability and wetting property.

The polymers need to possess sufficient tensile, shear and peel strengths.

The polymer should be economical and readily available.

Polymers should be tasteless.

It should be inexpensive and readily available¹⁰.

Plasticizers (<20%)

Plasticizer is a key ingredient influencing the strength of the orodispersible films. It enhances mechanical properties such as tensile strength and elongation to the film. It also reduces brittleness of the strip as a result improves its flexibility. The choice of plasticizer will rely upon its compatibility with that of the polymer and also nature of the solvent employed in the casting of the strip. Propylene glycol (PG), polyethylene glycol (PEG), glycerol, 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 plasticizers. Glycerol tends to provide a better plasticizing capacity for films. Improper use of plasticizer may lead to blooming, film cracking, splitting and peeling of the strip^{10,11}.

Saliva stimulating agent

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 FDF. Generally acids which are used as salivary stimulants citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants and citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%.

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 polaxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, spans, benzalkonium chloride, etc. Out of these most predominantly used surfactant is polaxamer 407^{11,12}.

SWEETENING AGENT

Sweeteners include both natural and artificial sweeteners as

Natural sweeteners include monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and their mixtures. Water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like and free acid form of saccharin and dipeptide based sweeteners. Aspartames, Neotame are successfully used for the taste masking¹².

Flavoring agent

The flavouring agent is required to mask the taste depends on the flavour type and its strength. Commonly employed are fruity flavours (vanilla, cocoa, coffee, chocolate, citrus), flavor 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.

Coloring agent

Generally incorporated colouring agents are FD and C colours, natural colours, pigments such as titanium dioxide etc^{12,13}.

Stabilizing and thickening agents

Stabilizing and thickening agents are employed before casting to improve the viscosity and consistency of dispersion or solution of the film preparation. Natural gums like xanthan gum, locust bean gum, carragenan and cellulosic derivatives are few examples of stabilizing and thickening agents. They are used in the concentration up to 5%w/w^{12,13}.

METHOD OF PREPARATION

Different methods for achieving fast dissolving film formulation by the following

1. Semisolid casting
2. Solvent casting
3. Hot melt extrusion.
4. Solid Dispersion Extrusion
5. Rolling method.

Semisolid casting

In this method at first a solution of water soluble 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.

Solvent casting

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

Hot melt extrusion

In the hot melt extrusion drug mixed with carrier in the solid form. Extruder having extra facility with heater it melt the solid form carrier and drug then this melt is place in the dies and cut in to specific shape.

E.g. Maltodextrin can be used to produce fast-dissolving films with a high drug loading capacity by hot-melt extrusion technology.

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 method

In this technique suspension or a solution containing drug is rolled on a carrier. The solvent utilized mainly is water or a mixture of water and alcohol. The films are dried on the heated rollers and sliced into desired shapes and sizes. Other ingredients such as API, polymer, plasticizer and other required ingredients are dissolved in small quantities of aqueous solvent utilizing the high-shear processor¹⁰⁻¹³.

Recent Manufacturing Technologies

XGel

This type of film is mostly preferred by vegetarians as the film is not made from sources of animals. It is used to mask the taste, the colour, the layer and they have enteric properties.

Wafertab

Wafer tab is one of the different processes to load a drug in then films for topical or oral administration. After casting into the films API ingredients are added to it. In this system in which drug is in the form of ingestible filmstrip, this technology gives quick dissolution and release of the drug when it comes in contact with saliva¹⁰⁻¹³.

Evaluation of Oral Films

Thickness

It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations. The thickness of the film should be in the range 5-200µm.

Dryness/ Tack Test

Dryness is the property to measure the solvent or water content present in the film whereas tack is the tenacity with which the film adheres to any piece of paper which is pressed into contact with the strip. Eight stages of film drying process have been recognized i.e. set-to-touch, dustfree, tack-free, dry-to-touch, dry-hard, dry-through; dry-to-recoat and dry print free.

Tensile strength

It is defined as the point at which the film breaks due to the application of maximum stress. This test is carried to determine the mechanical strength of the ODF. The tensile strength can be calculated by the equation.

Tensile strength= (failure load/strip thickness ×width of strip) ×100

Swelling property

By using simulated saliva solution, the swelling studies of film are carried out. Weighed every film sample and placed in pre-weighed stainless steel wire mesh. The mesh is dissolved in 15ml medium in plastic container. Determine increase in weight film at present time interval until constant weight is achieved.

The degree of swelling was calculated using parameters:

$$\alpha = \frac{wt - w_0}{w_0}$$

wt = weight of film at time t

w₀ = weight of film at time zero

Folding endurance

Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value¹¹⁻¹⁴.

Transparency

The transparency of the film can be determined using a simple UV spectrophotometer. Cut the film specimen into a rectangle and placed on the internal side of the spectrophotometer cell. The transmittance of the film is determined at 600nm. The transparency of the film is calculated as follows:

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

Where T₆₀₀ is transmittance at 600nm
b is the film thickness, c is concentration

Contact Angle

Goniometer determined the contact angle at room temperature. Put a drop of double distilled water on dry film surface. Images of water droplet were recorded within 10 sec of deposition by means of digital camera. The contact angle was measured on both side of drop and average is taken.

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%.

Disintegration time

A disintegration of orally fast dissolving films requires USP disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER 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 strips¹²⁻¹⁵.

In-vitro dissolution test

Commonly USP I (basket) and USP II (paddle) are to carry out the test. In the *in vitro* dissolution process sink condition should be maintained sometime during the test ODF's floats on the medium. So there is difficulty in performing the test in proper way. This issue is mostly faced by the USP II apparatus. The phosphate buffer 300ml of PH6.8 and 900 ml of 0.1N Hydrochloride is used as media Temperature maintained at 37 ± 0.5°C. Generally 50 rpm of rotation speed is maintained samples are taken at the intervals and analyzed in Ultra Violet Spectrophotometer. Despite its expansive use dissolution test is still prone noteworthy inaccuracy and tests let down. Recently they have carried out new bio-relevant *in vitro* dissolution test for oral dispersible film.

CONCLUSION

The fast dissolving oral films are considered as the novel work in the pharmaceutical field, this approach of delivery system is best suited for geriatric, paediatric and psychiatric patients who have difficulty in swallowing, so this approach exhibits less risk and improved patient compliance with higher safety. Since FDF's bypasses the hepatic metabolism, its ease of administration and requires no water at the time of drug administration makes this delivery a unique one, and improves the therapeutic response significantly.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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