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FAST DISSOLVING ORAL FILMS: AN INNOVATIVE DOSAGE FORM FOR SYSTEMIC DRUG DELIVERY

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Fast dissolving films, Solvent casting, Semisolid casting, Disintegration time

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ABSTRACT

Today, fast dissolving oral films (FDOF) are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs. Fast dissolving films are solid oral dosage form, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or chewing. The drug delivery systems allow the medication to bypass the first pass metabolism there by making the more bioavailable. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing and eliminate patients fear of chocking. Fast dissolving film are manufacture by solvent casting, semisolid casting and hot melt extrusion. Solvent casting being the most preferred offers great uniformity of thickness and films have fine gloss and better physical properties. Oral films are evaluates for various attributes such as thickness, folding endurance, disintegration and dissolution time. This review supported to describes about the formulation methodology, evaluation parameters and the future aspects of oral fast dissolving films.

INTRODUCTION

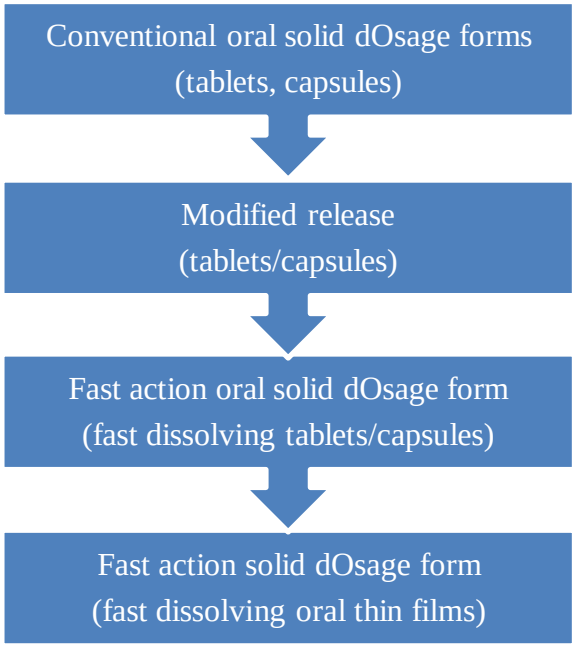
Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients[1,2].About 60% of all dosage forms are available in the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance.

Fast dissolving film is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration. Fast dissolving films (FDFSs) are the most advanced form of oral solid dosage form as they improve the efficacy of APIs by dissolving within a minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration[2][3].It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa which is 4-1000 times greater than that of skin [4][5][6].

FDFSs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, 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. This newly developed 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 [2].New addition drug in the odf preparations are Metoclopramide (5mg), Dextromethorphan HBr, Diphenhydramine HCl, Simethicone, Phenylephrine HCl, Benzocaine Menthol[7], Nicotine (Nicabate film)[8].

Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/ capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral films. Basically the Odf can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other excipients. The advantages of convenience of dosing and portability of have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.[2]

Flow Chart for the Development of Oral Solid Dosage form:



Comparison between orally fast dissolving films and oral disintegrating tablets [9]

Table:1

Orally Dissolving Films (odf\Os)	Oral Disintegrating Tablets(odt\fdt)
Larger surface area gives greater dissolution	Less surface area gives less dissolution than odf
Odf are flexible and durable	Odt are brital and less durable than odf
only Low dose can incorporated in formulation	High dose can incorporated in formulation
Odf thickness are 50 to 500 µm	Odt thickness as like convention tablet
Patient compliance more	Patient compliance is less than odf

Advantages of oral disintegrating films:

1) Rapid disintegration than oral disintegrating tablet due to larger surface area.
2) Oral disintegrating tablet are having fragile and brittle nature due to they having special packing against the transport, but odf having flexible films they not having the fragile nature.
3) Odf are the recently formed material which are majorly accepted for the OTC counter than conventional product because having accurate dosing in the safe and effecious format and no need of water when it taken.
4) Patient of dysphasia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

5) Those drug having first pass hepatic metabolism odf having advantage over them because oral or buccal mucosa is highly vascularised, that's why drug are absorbed directly in to the systemic circulation.
6) Avoidance of first pass effect drug should be the improve potency by the sublingual or buccal route with low dose high efficacy and less side effect.[7]
7) With respective drops, syrup the precision is more about the dose in the oral disintegrating films. Taste masking of drugs should be done.

Disadvantage of oral disintegrating films:

1) High dose is not incorporated in the ODF formulation.
2) Films are temperature and moisture sensitive that's why special type packing is needed.
3) Uniformity in dose is technical problem.

Ideal characteristics of a drug to be selected:

1) The drug should be pleasant taste.
2) The drug should be preferably have a dose up to 40mg.
3) The drug should have small or moderate molecular weight.
4) They should have good stability and solubility in water and in saliva.
5) It should be partially unionized at the pH of oral cavity.
6) It should have the ability to permeate oral mucosal tissue.

Formulation considerations:

Formulation of FDFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of oral strips should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

The area of drug loaded film should be between 1-20 cm2 which depends on the amount of water-soluble polymers that are responsible for rapid disintegration.

Table:2 Following General Composition of Drug & Excipients In Percentage[11]:

Sr. no	INGREDIENTS	CONCENTRATION (%)
1	Drug	5-30
2	Water soluble polymer	40-50
3	Plasticizer	0-20
4	Sweetening Agent	3-6
5	Saliva stimulating agent	2-3
6	Surfactant/ Disintegrant	q.s
7	Fillers, colour and Flavours etc.	q.s

1) Drugs:

The FDF technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in FDF. Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated inthe FDF[12].Whilewater soluble APIs are present in the dissolved state in the FDF or in the solid solution form, the water insoluble drugs are dispersed uniformly in the strip. The distribution of water insoluble molecules in water miscible polymer becomes important from the large scale manufacture point of view. APIs can also be added as milled, micronized or in the form of nanocrystals or particles depending upon the ultimate release profile desired. 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 FDF. [13]

Several class of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole), antiasthamatics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. paracetamol, meloxicam, valdecoxib).[14] [15]

Table 3 Below List of few drug that can be incorporated in fast dissolving film

Drug	Dose	Therapeutic Action
Azatidine Maleate	1mg	Anti histaminic
Nicotine	2mg	Smoking cessation
Loperamide	2mg	Anti diarroheal
Ondensetron	2.5mg	Anti emetic
Triplodine hydrochloride	2.5mg	Anti histaminic
Zolmitritpan	2.5mg	Anti migraine
Salbutamol	4mg	Anti histaminic
Chlorpheniramine Maleate	4mg	Anti allergic
Cetrizine	5-10mg	Anti histaminic
Ketoprofen	12.5mg	Analgesic
Dicyclomine hydrochloride	25mg	Muscle relaxant

2) Water soluble polymers

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. 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 polymer film bases. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium

Alginate, Hdroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and EUDRAGITRD108,9,10,11,12.Eudragit RL100.Polymerized resin is a novel film forming polymer.[16]

3) Plasticizers

Formulation considerations (plasticizer, etc.) 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, di butyl pthallate, and polyethylene glycols etc.[17]

4) Surfactants

Surfactants are used as solublising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent[18]

5) Flavour

Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors. *Some saliva stimulating agents may also be added toenhance the disintegration and to get rapid release. Some of these agents are citric acid, tartaric acid, malic acid, ascorbic acid and succinic acid[19].

6)Coloring agents

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in oral strips when some of the formulation ingredients or drugs are present in insoluble or suspension form.

Method of Preparation:

Different methods for archiving odf formulation by following method [20] [21]

1) Casting and drying
    A) Solvent casting
    B) Semisolid casting.
2) Freeze dried wafer
3) Extrusion
    A) Hot melt extrusion.
    B) Solid dispersion Extrusion
    C) Rolling method.

Generally for formulation of odf we are using the solvent casting method and extrusion method. Their method of Descriptions is given below.

Solvent Casting Method:

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

Advantage:

- Great uniformity of thickness & great clarity than Extrusion.
- Films have fine gloss& freedom from defect such a die lines.
- Films have more flexibility & better physical properties.

Disadvantages:

- The polymer must be soluble in a volatile solvent or a stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

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 film 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 to film forming polymer should be 1:4.

Hot Melt Extrusion:

In this method drug is mixed with carriers in solid form. Extruder having heaters that melts the mixture of drug and carrier material. Finally the melted mixture is shaped in films by dies.

Advantages:

- Without use of any solvent or water and consists of fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages

- Thermal degradation due to use of high temperature
- Limited number of available polymers and flow properties of the polymer are essential for processing
- All excipients must be devoid of water or any other volatile solvent

Solid Dispersion Extrusion:

Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method:

In this method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and gives desired shape and sizes.fig-1

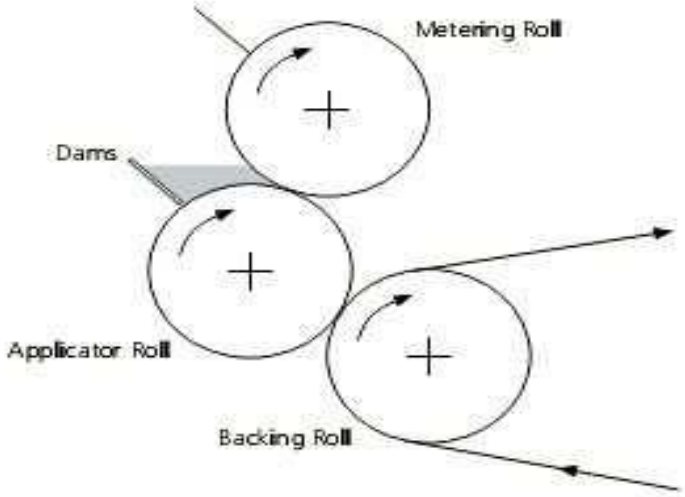


Fig-1. Three roll coating unit

Quality Control Test For Fast Dissolving Film [1][2][24]

1) **Morphology Study:**

The morphological study of oral strip is done by the scanning electron microscopy (SEM) at a definite magnification. Study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API.

2) **Weight Variation:**

Weight variation is studied by individually weighing 10 randomly selected films and by calculating the average weight.

3) Assay/drug content and 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%.

4) Thickness:

As the thickness of film is directly concern with drug content uniformity so 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 3 or 5 strategic locations.

5) Dryness test/tack tests:

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 also available for this study.

6) 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:

Tensile strength = Load at failure × 100 / Strip thickness × Strip width

7) 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 content increases.

% Elongation = Increase in length ×100 / Original length

8) 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 as follows:

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Young's modulus = Slope × 100 / Strip thickness × Cross head speed

9) 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 51 mm (2 in)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or 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).[22]

10) **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.

11) **Disintegration Time:**

The disintegration time limit is of 30sec or less for orally disintegrating tablets, as described in CDER guideline and can be applied to fast dissolving oral film. No official guideline is available for oral fast dissolving films. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for film is 5-30 sec. Although, no official guidance is available for oral fast disintegrating films strips.[23]

12) **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 which is then submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weigh was observed. The degree of swelling was calculated using parameters

$$\alpha = (wt - wo)/wo$$

where, Wt is weight of film at time t, and wo is weight of film at time zero.

13) **Dissolution test:**

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.

CONCLUSION

Fast dissolving films are considered to be the most advanced, innovative and promising dosage forms as they help in the effective management of immediate attacked diseases. Bypassing the hepatic first pass metabolism, fast dissolving films increase the bioavailability of the medication and moreover they are of more patient compliance. They have great potential of delivering the medicinal agent systemically as well as locally and have several advantages over many conventional dosage forms thus emerging as a new novel drug delivery system. As the future of fast dissolving films is expected to grow at a blistering pace day-by-day, more and more of scientific research work can be contributed for the further development in this particular arena of pharmaceutical drug delivery systems.

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