

Review Article



Fast Dissolving Oral Thin Films: An Effective Dosage Form for Quick Releases

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ABSTRACT

Oral route is one of the most preferred routes of drug administration because of low-cost and ease of administration increases the patient compliance. Many patients especially geriatric and paediatric have difficulty to swallow the tablets and hard gelatine capsules. Fast dissolving drug delivery systems (FDDDS) were developed as an alternative to tablet, capsule and syrups. Among this, fast dissolving oral thin-films are useful in patients such as paediatric, bedridden or developmentally disabled, geriatric, who face difficulty in swallowing tablets or hard gelatine capsules. Oral fast dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which rapidly disintegrate or dissolves on tongue or in the buccal cavity. It is an alternative platform for molecules that undergoes high first pass metabolism. The present review gives an account of different formulations, methods of preparation and quality control of the fast dissolving oral thin films.

Keywords: First pass metabolism, hydrophilic polymers, fast dissolving oral thin films, Patient compliance.

INTRODUCTION

Among the drug delivery routes, oral route is one of the most convenient, cost-effective and preferred route of drug administration.¹

But some patients, especially paediatrics and geriatrics have difficulties in swallowing or chewing some oral solid dosage forms like tablets and hard gelatine capsules.

Because of the fear of choking, they are unable to take these dosage forms. In order to overcome this, several fast dissolving drug delivery systems (FDDDS) came into existence.²⁻⁴ Buccal drug delivery is an important route of drug administration.

Problems such as high first pass metabolism and drug degradation in the gastrointestinal environment can be avoided by administering the drug through buccal route.

Research in the oral drug delivery system has led to the advancement 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 oral thin films.⁵⁻⁷

Fast dissolving oral thin films is an ultra thin film that employs a hydrophilic polymer that rapidly hydrates or adheres when placed on the tongue or in the buccal cavity.⁸

These films disintegrate or dissolve within seconds to release the active agent without drinking and chewing.^{9,10}

As the mucosa is highly enriched with blood supply, it provide quick absorption and instant bioavailability of drugs.^{11,12}

The instant bioavailability results from bypassing first pass metabolism. So they are generally designed for the

drugs having high first pass metabolism for achieving better bioavailability.^{13,14}

The oral thin-film technology is still in the beginning stages and has bright future ahead because of patient compliance.^{15,16}

Advantages^{17,18}

- Avoiding the risk of choking
- Avoid first pass metabolism and provide quicker onset of action at lower doses.
- Palatable
- Good stability
- No requirement of water
- Large surface area provides rapid disintegration and dissolution in the oral cavity.
- Ease of administration of film to the patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders
- Dose precision

Disadvantages¹⁸

- Drugs with high dose cannot be incorporated into the film
- Drugs which causes irritation to the mucosa cannot be administered
- As it is fragile and must be protected from water, it requires special packaging

Types of Fast Dissolving Oral Films¹⁸

There are three different subtypes



1. Flash release
2. Mucoadhesive melt release
3. Mucoadhesive Sustained release

Structure of Oral Mucosa¹⁹

Oral mucosa contains following three layers of cells

- Stratified squamous epithelium** - It's the outermost layer of the oral cavity. Basement membrane is the interface between connective tissue and epithelium
- Lamina propria** - It's a connective tissue present below basement membrane
- Sub mucous membrane** - It is the innermost layer of the oral cavity.

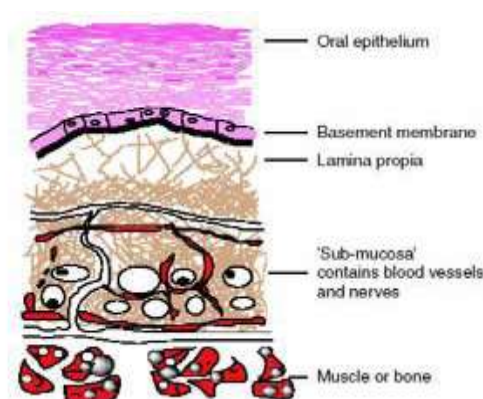


Figure 1: Structure of oral mucosa

Standard Composition of Oral Fast Dissolving Film^{20,21}

Oral dissolving film is a thin film having an area of 5-20 cm² containing drug. The drugs can be loaded up to a single dose of 30 mg. From the regulatory perspectives, all the excipients used in the formulation must be generally regarded as safe (i.e. GRAS-listed) and must be approved for use in oral pharmaceutical dosage forms.

A typical formulation contains the following ingredients

1. Drug
2. Film forming polymers
3. Plasticizers
4. Saliva stimulating agent
5. Sweetening agent
6. Flavouring agent
7. Surfactant
8. Colors, Filler

Table 1: Concentration of Component^{20,21}

S. No.	Ingredients	Concentration
1	Drug	1-30%
2	Film forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Flavouring agent	Q. S.
7	Surfactant	Q. S.
8	Colors, Filler	Q. S.

Active pharmaceutical ingredient^{20,21}

A typical film contains 1-30% w/w of the active pharmaceutical ingredient. For the effective formulation, it is essential to incorporate micronized API since it enhance the texture of film and provide rapid dissolution and uniformity in the fast dissolving film.

Several class of drugs can be formulated as mouth dissolving films including paediatrics (anti-tussive, expectorants, anti-asthmatics), geriatrics (antiepileptic, expectorants), gastrointestinal diseases, nausea (e.g. due to cytostatic therapy), pain (e.g. migraine), CNS (ex. Anti Parkinsonism therapy).

Table 2: Examples of suitable drug molecule and its category²⁰⁻²²

Category	Examples
Anti-emetics	Ondansetron, Granisetron, Plonasetron, Dronabinol, Aprepitant, Ramosetron, Trimethobezamide, Nabilone, Metoclopramide, Dolasetron, Dimenhydramine
Serotonin inhibitors	Fluoxetine, Setraline, Paroxetine, Fluxoamine, Citalopram and Alaproclate
5HT3 antagonists	Alosetron, Ondansetron, Granisetron, Palonosetron, Rmosetron and Tropisetron
Anti-epileptics	Carbamezapine, Clonazepam, Diazepam, Divalproex sodium, Fosphenytoin, Gabapentin, Lamotrigine, Levetiracetam, Oxacarbazepine, Phenytoin, Primidone and Valproate sodium
Anti-migraines	Almotriptan, Dihydrogotamine Mesylate, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan and Zolmitriptan
Dopamine D1 and D2 antagonists	A misulpride, Bromperidol, Cabergoline, Domeperidone, Fenoldopam, Halopiridol, Metoclopramide, Metopimazine, Pergolide Mesylate, Prochlorperazine, Quetiapine, Ropinirole Hydrochloride, Sulpiride, Tiapride and Zotepine
No tropics	Almitrine Dimesylate and Raubasine, Cevimeline Hydrochloride, Codergocrine Mesylate, Donepezil, Galantamine, Ginkgo Biloba Extract (Egb 761), Memantine, Nicergoline, Piracetam, Rvastigmine, Tacine And Vinpocetine
Statins	Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin and Simvastatin

Table 3: Examples of natural and synthetic polymers²⁸

S. No	Polymer	Examples
1	Natural polymers	Pullulan, Starch, Gelatin, Pectin, Sodium alginate, Maltodextrin, Polymerized resin, Lycoat NG73, Xanthan
2	Synthetic polymers	Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Polyethylene oxide, Hydroxy propyl cellulose, Polyvinyl pyrrolidone, Poly vinyl alcohol, Hydroxy ethyl cellulose, Kollicoat

Table 4: Examples of natural and artificial sweeteners³⁶

S. No	Sweeteners	Examples
1	Natural sweeteners	xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids
2	Artificial sweeteners	First generation- Saccharin, cyclamate and aspartame Second generation- acesulfame-K, sucralose, alitame, neotame

Table 5: Examples of Flavouring agents³⁶

Flavour oils	Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg
Fruity flavours	Vanilla, cocoa, coffee, chocolate and citrus
Fruit essence type	Apple, raspberry, cherry, pineapple

Table 6: Advantages and disadvantages of solvent casting method^{40,41}

Advantages	Disadvantages
Greater uniformity of thickness and much clarity than extrusion.	The polymer must be soluble in a volatile solvent or water.
Film has fine gloss and freedom from defects such as die lines.	Viscosity should be formed so that the solution must be stable with a reasonable minimum solid content
More flexibility and better physical Properties	Formation of a homogeneous film and release from the casting support must be possible.
Finished film in thickness is typically 12-100 µm	

Table 7: Advantages and disadvantages of Hot melt extrusion method⁴⁰⁻⁴³

Advantages	Disadvantages
Better method for poorly soluble drugs	Use of high temperature may cause thermal degradation
Lower processing steps	Flow properties of the polymer are necessary for processing.
More uniform dispersion because of intense mixing and agitation	All the excipients should be free from water or any other volatile solvent
Less energy compared with high shear methods.	Limited availability of polymers

Film forming polymers²³⁻²⁷

Water-soluble polymers are used as film formers since they achieve rapid disintegration, good mouth feel and mechanical properties to the films. In order to obtain the desired film properties like hydrophilicity, flexibility, mouth feel and solubility, polymers can be used alone or in combination with others. By increasing the molecular weight of polymer film bases, the rate of disintegration of polymers decreases.

The polymers employed in oral thin films should be:

- Non-toxic and non-irritant
- Devoid of leachable impurities

- Good wetting and spread ability property
- Exhibit sufficient peel, shear and tensile strengths.
- Readily available
- Inexpensive
- Water soluble with low molecular weight
- Excellent film forming capacity
- Should have good shelf life

Currently, both natural and synthetic polymers are used as film forming agents. Table 3 shows various natural and synthetic polymers used in fast dissolving oral thin films.

Plasticizers²⁹⁻³³

It is an important ingredient of oral thin films. The plasticizers help to improve the mechanical properties of film such as tensile strength and elongation to the film. It also reduces the brittleness of the film. It may improve the flow and enhances the strength of polymer. The proper selection of the plasticizers is very important. It should be compatible with the drug, polymers as well as with the other excipients. The improper selection may cause cracking, splitting and peeling of the film. The commonly used plasticizers are glycerol, propylene glycol, polyethylene glycol, dimethyl, dibutyl, diethyl phthalate, tributyl, triethyl, actyl citrate, triacetin and castor oil.

Saliva stimulating agent^{33,34}

The purpose of using saliva stimulating agents is to increase the rate of production of saliva so that the oral film disintegrate and dissolve faster in the oral cavity. It can be used alone or in combination in the range of 2-6%. Commonly used saliva stimulating agents are citric acid, malic acid, lactic acid, ascorbic acid, tartaric acid. Among this, citric acid is the preferred one.

Sweetening agents³⁴⁻³⁶

Generally, sweeteners are used to mask the bitter taste of certain drugs. Both natural and artificial sweeteners can be used alone or in combination. Table 4 shows various natural and artificial sweeteners used in fast dissolving oral thin films.

Flavouring agent³⁶

They impart flavour to the formulation. It can be selected from synthetic flavour oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers.

It can be used alone or in combination. The amount of flavour required to mask the taste depends on the flavour type and its strength.

Surfactant^{37,38}

They are generally used to increase the solubility, wettability and dispersability of the film so that the film gets dissolved within seconds and release the drug fastly. Commonly used surfactants are sodium lauryl sulphate; surfactants are polaxamer 407, benzalkonium chloride, benzathonium chloride, tweens etc.

Colouring agents^{38,39}

Pigments like silicon dioxide, titanium oxide or FD&C approved coloring agents are most commonly used. Their concentration level should not exceed 1%.

Methods of Preparation⁴⁰

The methods for the preparation of fast dissolving oral thin films are

- Solvent casting method
- Semisolid casting method

- Hot melt extrusion method
- Solid dispersion extrusion method
- Rolling method

Among this, the most commonly used industrial methods are solvent-casting method and Hot melt extrusion

Solvent casting method^{40,41}

Water soluble polymers and plasticizers are dissolved in a suitable volatile solvent like Ethanol or distilled water to form a clear viscous solution

Solution is stirred for 2hrs in the magnetic stirrer and kept aside

API and other ingredients are dissolved in aqueous solvent and are combined with the bulk

The entrapped air is removed by vacuum

Finally the solution is casted into a suitable Petri dish and dried in an oven at 50 °C for 24 hrs

Film is cut into desired size and shape

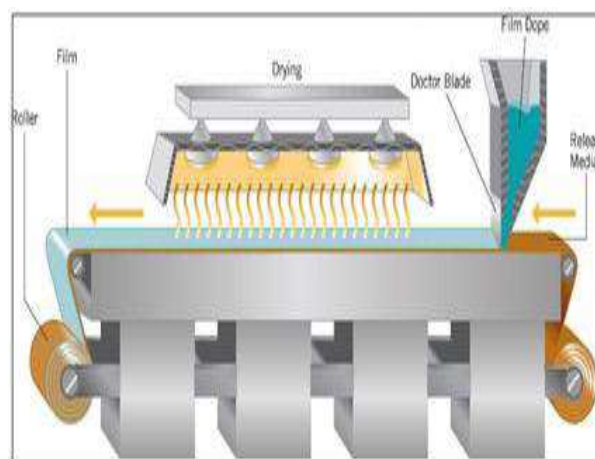


Figure 2: Solvent casting method.⁴⁰

Semisolid casting method^{40,41}

Solution of water soluble film forming polymer is prepared

It is poured into the solution of acid insoluble polymers in the ratio of 1:4 (e.g. cellulose acetate phthalate, cellulose acetate butyrate)

A gel mass is obtained by the addition of relevant amount of plasticizer

It is casted into the films or ribbons by using heat controlled drums.

The thickness of the film should be about 0.015-0.05 inches

Hot melt extrusion method⁴⁰⁻⁴³

It is usually used to prepare granules, sustained release tablets, transdermal and transmucosal drug delivery systems.

Initially the drug is mixed with carriers in solid form
 Melt the mixture by the extruder having heaters
 Finally the melt is shaped into films by the dies

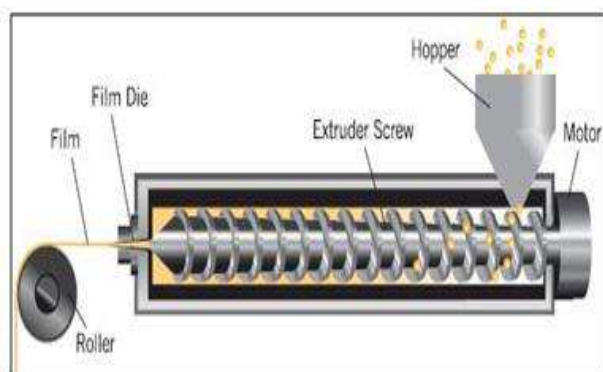


Figure 3: Hot melt extrusion method.⁴⁰

Solid dispersion method⁴¹⁻⁴³

In this method, in the presence of amorphous hydrophilic polymers, one or more active ingredients are dispersed in an inert carrier in a solid state.

API is dissolved in a suitable solvent to obtain a solution

Solution is added into the melt of suitable polymer (PEG) below 70 °C without removing liquid solvent

Finally by a means of dies, solid dispersion are shaped into films

Rolling method^{44,45}

Initially a pre-mix is prepared by film forming polymers, polar solvent and other additives except a drug

Add required amount of drug to the pre-mix

The drug is blended with pre-mix to obtain uniform matrix

The mixture obtained is fed into the roller

Film is formed and carried away by support roller

Wet film is then dried using controlled bottom drying

Film is cut into desired size and shape

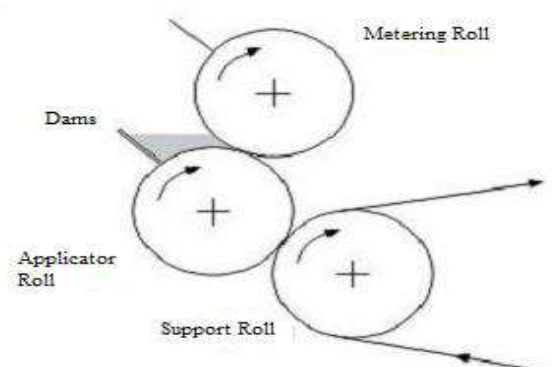


Figure 4: Rolling method⁴⁰

Evaluation Parameters^{46,47}

Mechanical Properties^{46,47}

- **Thickness test:** Thickness specifies the dose accuracy of drug in the film. It is measured by a micrometer screw gauge or calibrated digital Vernier callipers at five different strategic locations and the mean value is calculated which indicates the final thickness of the film. The thickness of the film should be in the range of 5-200 µm.
- **Dryness / tack test:** Tack is defined as the tenacity with which the strip gets adhered to an accessory like a piece of paper that has been pressed into contact with strip. Eight stages of film drying process have been identified and these are set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through (dry to handle), dry to recoat and dry print free. Various instruments are available to perform this test.
- **Tensile strength:** It is the maximum stress applied to a point of film at which the strip specimen breaks. A film should have good tensile strength. Weight at which the film breaks is known as load failure. Tensile strength is calculated by the applied load at rupture divided by the cross-sectional area of the strip.

$$\text{Tensile Strength} = \frac{\text{Load at failure} \times 100}{\text{strip thickness} \times \text{strip width}}$$

- **Percent elongation:** Whenever a stress is applied on the film, it starts stretching and it is called strain. Strain is the deformation of the film divide by the original dimension of the film. It directly depends upon the plasticizer added. As the amount of plasticizer increases, percentage elongation of the film also increases.

$$\% \text{ elongation} = \frac{\text{Increase in length of film} \times 100}{\text{Initial length of film}}$$

- **Young's modulus:** It is the measure of stiffness of the strip. It is the ratio of applied stress over strain in the region of elastic deformation. Films which are hard and brittle in nature have high tensile strength and young's modulus.

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{strip thickness cross} \times \text{head speed}}$$

- **Tear resistance:** It is the maximum resistance required to tear the film. A very low rate of load of 51 mm/min is applied. Its unit is Newton or pounds-force.
- **Folding endurance:** It indicates the brittleness of the film. It can be done manually, as the number of times the film folded without breaking or without any visible crack.

Organoleptic test^{46,47}

As the film disintegrates in the oral cavity, it should have acceptable organoleptic characteristics like colour, flavour and taste.

An oral thin film should have attractive colour as they are administered to children and should be uniform. Flavours used in the formulation should provide good odour and should mask the taste of polymer, drug and other excipients. Taste is an important factor in patient acceptance. Specially controlled taste panels are used for the physical evaluation. Electronic tongue technique is also used which is based on the principle of potentiometric titration method.

Surface pH test^{46,47}

Surface pH of film may cause irritation to the oral mucosa. It is necessary to check the surface pH of the film. Surface pH of the film should be neutral i.e. 7 or should be close to 7. A combined pH electrode can be used for this purpose. The film is made slightly wet with water and the pH is measured by bringing electrode in contact with film and the pH reading is noted. This test is applied on at least 6 films and the mean \pm SD can be calculated which the final value of surface pH. There is one more method to determine the surface pH i.e. 1.5%w/v agar gel is prepared and the prepared films were placed on it. The surface pH can be measured using pH paper. It is placed on the surface of the film and change in colour of pH paper gives the value of surface pH of the film.

Contact angle^{46,47}

It gives the information about wetting behaviour, disintegration time and dissolution of oral film. This can be performed with the help of goniometer at room temperature. For this purpose, double distilled water should be used. A dry film is taken and a drop of double distilled water is placed on surface of the dry film. Images of water droplet are taken by a means of digital camera within 10 s of deposition. Digital pictures should be analysed by image J 1.28v software (NIH, USA) for angle determination.

Transparency^{46,47}

A simple UV spectrophotometer is used to determine the transparency of the film. Film is taken and is placed on the internal side of spectrophotometer cell and analysed at 600 nm. Transparency can be calculated by using the following formula:

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

Where

T_{600} = Transmittance at 600 nm

B= film thickness (mm)

c = concentration

Assay/drug content uniformity^{46,47}

This is carried out by any standard assay method described in any of the standard pharmacopoeia for the particular drug. It is determined by estimating the drug content in individual film. The limit of content uniformity is 85-115%.

Permeation studies^{46,47}

To study the permeability, Modified Franz diffusion cell can be used along with porcine buccal mucosa. This cell consists of a donor and a receptor compartment. Between the two compartments, mucosa is placed (size of the mucosa should be the same size as that of the head of receptor compartment). Then, the receptor compartment is filled with buffer (pH 6.8) and maintained at $37 \pm 0.5^\circ\text{C}$. The donor compartment should consist of 1 ml simulated saliva fluid of pH 6.8. In order to maintain thermodynamics, a magnetic bead stirrer at a speed of 50 rpm is used. With a few drops of simulated saliva, film is moistened and should be kept in contact with mucosal surface. At a particular time interval, sample are withdrawn and replaced by same amount of fresh medium. The percentage of drug permeated can be determined by suitable analytical method.

Scanning electron microscopy^{47,48}

Scanning electron microscopy is an important method to study the surface morphology of the film between different excipients and drug. A film sample is taken and placed in sample holder and at $\times 1000$ magnification and various photomicrographs were taken using the tungsten filament as source of electron.

In vitro disintegration test^{47,48}

It is the time at which the film breaks or disintegrates when brought in contact with water or saliva. This test is carried out by placing the film in the phosphate buffer. United State Pharmacopoeia (USP) disintegration apparatus can be also used to study the disintegration time. The disintegration time should be in the range of 5-30 sec.

In-vitro dissolution test^{47,48}

Amount of drug substance that goes into the solution per unit time under standard conditions of temp, solvent concentration and liquid/solid interface is called dissolution. A standard basket or paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing. When paddle type dissolution apparatus is used, it's difficult to perform dissolution study of oral film as they can float over the dissolution medium. Selection of the dissolution media depends on the sink conditions and the highest dose of drug.

During dissolution study, the temperature of the medium should be maintained at $37 \pm 0.5^\circ\text{C}$ and rpm at 50.

Stability studies⁴⁹⁻⁵¹

Stability testing of the prepared formulation is mainly done to check whether it is a stable product or not.

It is also used for the determination of effect of temperature and humidity on the stability of the drug for the proper storage, initially the formulation is wrapped in a butter paper followed by aluminium foil wrapping over it, then this is packed in an aluminium pouch and heat sealed.

Formulation should be stored at 45°C / 75 % RH for 3 months. During the period of stability studies, triplicate samples are taken at three sampling intervals i.e. 0, 1 and 3 month and films should be evaluated for physical changes and drug content.

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