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Kuldeep Chaturvedi, Pravin Kumar Sharma, Sumeet Dwivedi, Ravi Sharma, Gajanan N. Darwhekar
Acropolis Institute of Pharmaceutical Education and Research, Indore (M.P.), India - 453771

Correspondence

Dr. Pravin Kumar Sharma
Professor,
Acropolis Institute of Pharmaceutical Education and Research, Indore (M.P.), India - 453771

Email: praveensharma910@gmail.com

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Fast Dissolving Oral Film: An Innovative Approach for Drug Delivery

Kuldeep Chaturvedi, Pravin Kumar Sharma, Sumeet Dwivedi, Ravi Sharma, Gajanan N. Darwhekar

ABSTRACT

The present review will provide an overview of orally fast dissolving films. The most popular oral dosage forms are oral fast-dissolving films, which dissolve in the mouth in a matter of seconds without the need for water consumption and provide a quick onset of action. Because of their flexibility and ability to comply with patients, these drug delivery systems are primarily used for pediatric and geriatric patients. They release the active pharmaceutical ingredient within the mouth as soon as they come into contact with saliva. A rapidly dissolving oral dosage form that can be used for drugs with low bioavailability and high first pass metabolism. Oral films are formulated using polymers, plasticizers, colors, flavors and sweeteners etc. Solvent casting, hot melt extrusion, rolling, and solid dispersion techniques are used in the production of the oral film. This review compiles the most recent developments in the formulation of fast-dissolving films and their evaluation metrics, such as thickness, disintegration time, folding endurance, and *in-vitro* dissolution. It also highlights some of the marketed products to demonstrate the market's demand for oral fast-dissolving films. Also, go over a few of the difficulties encountered during the creation of fast-dissolving films.

Key words: Fast dissolving film, Solvent casting method, film forming polymer, Evaluation.

1. INTRODUCTION

One of the most popular methods for administering medications is orally since it is more affordable, convenient, and easy to administer, all of which increase patient compliance. The oral route presents challenges due to the inability of older and pediatric patients to swallow and their fear of choking. Research focused on patient convenience and compliance has led to the development of safer and more modern drug administration methods. Fast dissolving drug delivery systems are one such example that has recently gained acceptance and appeal. It offers more options for the consumer, dissolves quickly in the mouth, absorbs quickly, and has improved bioavailability. It may also be used for self-administration even in the absence of water.[1]

In order to help juvenile and elderly patients who had trouble swallowing pills and capsules, the quick dissolving drug delivery method was originally developed in the late 1970s. Drug administration through the buccal route has grown in importance recently. Numerous bioadhesive mucosal dosage forms have been created, including adhesive tablets, gels, ointments, patches, and, more recently, the use of polymeric films—also referred to as rapid dissolving films—for oral administration.[2]

1.1 Phases Involved In The Formulation of Oral Solid Dosage Forms

The formulation for solid oral dose form has through a number of stages of development that are shown in figure 1.

1.2 Anatomy of The Oral Cavity

To comprehend the environment created for medication delivery, the physiology and anatomy of the mouth cavity are investigated in figure-2. Drugs can avoid first-pass metabolism and enter the bloodstream straight through the oral mucosa. The epithelium of the mouth and the skin are quite similar, with a few minor variations in terms of keratinization, protection, and the lubricating mucus that covers the surface. Oral mucosa permeability is 4-1000 times higher than skin permeability. The oral cavity is divided into two regions: outer being the oral vestibule bounded by the lips and cheeks; the hard and soft palates, the mouth's bottom and tonsils.[3]

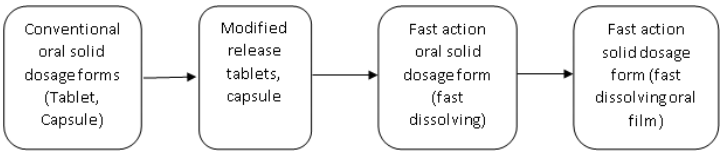

Figure 1- phases involved in the formulation of oral solid dosage forms

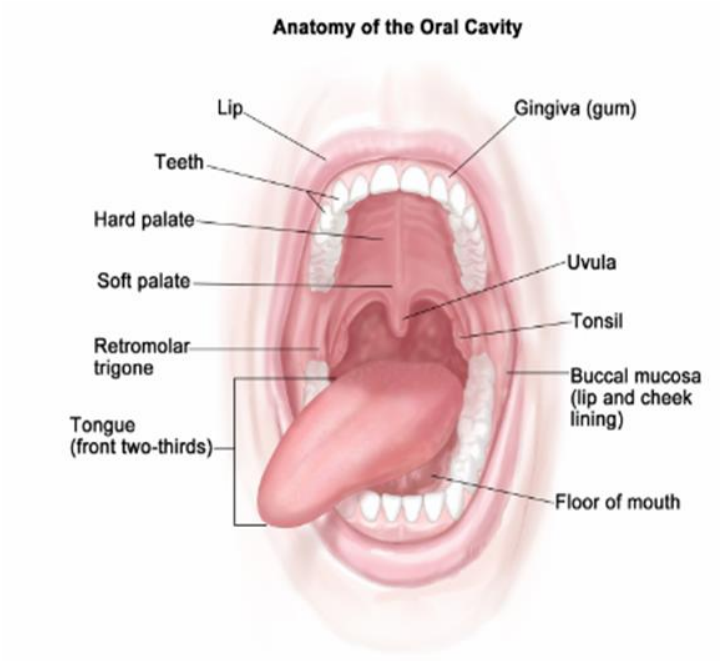

Figure 2- Anatomy of the mouth cavity

1.3 Advantages of Fast Dissolving Films

- Convenient dosing
- No water needed
- No chance of choking
- Taste masking
- Enhanced stability
- Improved patient compliance
- When the drug enters the bloodstream, its hepatic first pass action is reduced
- Local and site-specific activities
- Facilitate quick dissolution and disintegration within the mouth cavity.[4]

1.4 Disadvantages of Fast Dissolving Films

- Not more than 40 mg of high doses can be used
- By nature, hygroscopic
- It is not appropriate for medications that irritate the oral pH and are not long-lasting
- It requires particular packaging for products
- It also concerns stability and safety.[5]

1.5 Special Feature of Fast Dissolving Film

- A film needs to be attractive and thin
- Comes in a various shapes and sizes
- It ought to fit into the mouth cavity with ease
- Need to be less sensitive to external factors like humidity and temperature
- Ought to feel good in the mouth
- Should be compatible with taste masking
- Need to break down quickly without water
- Quick release.[6]

1.6 Ideal Qualities for A Promising Medication Candidate

- The medication should have a pleasant taste
- Drugs have been incorporated at a low dose of a maximum of 40 mg
- The molecular weight of drugs is smaller and moderate.
- Drugs have been well-stabilized and soluble in both water and saliva
- Medication has been partially unionized at the pH of the oral cavity
- It need to be able to penetrate the oral mucosal tissue.[7]

2. TECHNOLOGICAL CLASSIFICATION FOR FAST-DISSOLVING SYSTEMS

Table 1 explains the three major categories into which oral dissolving technologies can be categorized.[8]

- Lyophilized systems
- Compressed tablet based systems
- Fast dissolving oral film

Table –1 Technological classification for fast-dissolving systems

Properties	Lyophilized system	Compact tablet-based technology	Fast dissolving Oral film
Composition	Solution or suspension of drug with excipients	Active pharmaceutical ingredient with super disintegrants	Drug-containing hydrophilic polymers with additional excipients
Utilized technology	Transformation into Lyophils	compression done directly	Extrusion using hot melt and solvents casting
Features	high porosity that permits fast breakdown and entry of water or saliva	Variations in the degrees of hardness and friability lead to different requirements for disintegration and packaging.	Extensive surface area causes quick disintegration
Packing	Pack of blisters	high-density bottles made of polyethylene	Multiple units on a blister card

3. CATEGORIZATION OF FAST DISSOLVING FILM

- Flash release oral films (quick release)
- Mucoadhesive melt-away wafers (Mucoadhesive wafers)
- Wafers with a mucoadhesive sustained release (Mucoadhesvie extended release wafer).[9]

The categorization of fast dissolving film is explained in table-2

4. FAST-DISSOLVING FILM COMPOSITION

Fast dissolving films composition are shown in table-3.

4.1 Active Pharmaceutical Ingredients (API)

The medication oral films that are chosen should have adequate stability in both saliva and water at low dosages. Micronized API is usually helpful since it enhances film's texture and promotes improved dissolution and homogeneity in oral fast-dissolving films. Medications such as antiasthamatics (Montelukast, Salbutamol Sulphate), antihistamines (Levocitrizine), antianginals (Verapamil), antiulcers (Omeprazole), antiemetics (Domperidone), expectorants, antitussives, and NSAIDs (Valdecoxib, Meloxicam, paracetamol) can all be prepared as mouth dissolving films.[12]

Table –2 Categorization of fast dissolving films with their properties.[10]

Property /Sub/Type	Flash Release films	Mucoadhesive Melt - away wafer	Wafers with a mucoadhesive sustained release
Area (cm^2)	2-8	2-7	2-4
Thickness (µm)	between 20 and 70	Between 50 and 500	Between 50 and 250
Structure	Single-layer film	One-layer or multiple-layer systems	several layers
Ingredients Excipients	Water Soluble polymers	Water Soluble polymers	Low solubility or insoluble polymers
Drug phase	Solid solution	Drug molecules in Solid or suspended form	Suspension, solid or dissolved /dispersed
Application	Tongue (upper mouth cavity)	chewing gum or buccal area	Gingival tissue, (other area of the mouth cavity)
Dissolution	Not more than 60 seconds	Breakdown in a few minute, forming gel	Maximum 8-10 hrs

4.2 Film Forming Polymer

Because the tensile strength of polymers varies depending on the kind and quantity of films used, choosing the right polymer is among the most crucial and significant factors in the successful manufacture of oral films. By weight, the polymer

must make up at least 45% of the total weight of the dry film.; however, 60%–65% of the polymer by weight is recommended to provide the required characteristics. To obtain the required film qualities, Polymers are useful singly or in combination. The film-forming polymers that are used in the oral cavity have to be water-soluble since oral films disintegrate and spread quickly there. The films that are obtained must also be strong enough to withstand damage while being transported and stored.[13]

Water soluble grades of cellulose ethers, polyvinyl alcohol, polysaccharides, polyvinylpyrrolidone K-90, polyethylene glycols, pullulan, gelatin, carboxy methyl cellulose cekol 30, hydroxy propyl methyl cellulose E-3 and K-3, methyl cellulose A-3, A-6, and A-15, pectin, sodium alginate, hydroxyl propyl cellulose, maltodextrins, and eudragit RD10, 2011. These polymers are frequently employed as film formers.

Table 3 - Standard composition of fast dissolving film[11]

Ingredients	Amount	Example
Drug	5-30% w/w	Antiallergic, antiemetic, etc
Polymer soluble in water	45% w/w	A-3, A-6, and A-15 methyl cellulose, HPMC E3, E5, and E15, as well as K-3, Pullulan, pectin, hydroxypropylcellulose, gelation etc
Plasticizers	0-20% w/w	Glycerol, dibutyl pthallate, polyethylene glycol etc.
Sweetening agents	3-6% w/w	Saccharin, cyclamate, and aspartame
Saliva stimulating agents	2-6% w/w	Citric acid, malic acid, lactic acid and ascorbic acid
Surfactants	q.s	Sodium lauryl sulfate, benzalkonium chloride, tween etc
Fillers, colors, flavors	q.s	FD and C colors, US FDA approved flavors

4.3 Ideal Properties of Polymer for Fast Dissolving Film

- The polymer that is utilized needs to be non-irritating and non-toxic
- It needs to be free of impurities
- It needs to have sufficient wetting and spreading capabilities
- The tensile strength and stress levels ought to be adequate
- It must to be affordable and easily obtainable
- Reasonable shelf life is required
- It shouldn't result in further infections in the oral mucosa or dental regions
- It should feel smooth in the mouth
- It shouldn't slow down the process of disintegrating.[14]

4.4 Plasticizer

Plasticizer is used to increase a film's flexibility and decrease its brittleness. Plasticizer lowers the polymer's glass transition temperature, improving the mechanical qualities of the film, such as tensile strength and elongation. Additionally, it makes the strip less brittle, which increases its flexibility. The kind of solvent that is utilized and how well it works with the polymer determine which plasticizer to employ. Phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, and citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin, and glycerol are a few of the plasticizers which are regularly utilized. When plasticizer is used improperly, the strip may peel, split, bloom, and shatter the film.[15]

4.5 Sweetening Agents

Sweeteners have become more important in fast dissolving film preparations that are intended to dissolve or disintegrate in the mouth. Sweeteners that are commonly utilized include isomaltose, polyhydric alcohols (sorbitol, mannitol), fructose, glucose, sucrose, and dextrose. Moreover, artificial sweeteners such as cyclamate, aspartame, saccharin, acesulfame K, sucralose, alitame, and neotame (second generation) can be utilized.[16]

4.6 Super Disintegrating Agent

When super disintegrate are included in oral film formulations, the combined action of swelling and water absorption causes fast disintegration. Super disintegrate provide absorption and swelling due to their high water absorption, which speeds up disintegration and breakdown. Strong contact with saliva is critical to breakdown *ex*- sodium croscarmellose, sodium starch glycolate, etc.

4.7 Saliva Stimulating Agent

The purpose of saliva stimulating agents is to increase saliva production, which aids in the rapid dissolution of formulations for rapid dissolving strips. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are a few examples of salivary stimulants. Citric acid is the most favored among them.

4.8 Surfactants

Surfactants support the quick disintegration of the film and quick release of the API by acting as dispersing or wetting agents. For example tween and sodium lauryl sulfate etc.[17]

4.9 Coloring Agent

FD&C colors, natural colors, pigments like titanium dioxide, etc are frequently used.[18]

4.10 Flavoring Agent

The kind and strength of the flavor determine how much flavoring is needed to cover it up. Fruity flavors (vanilla, cocoa, coffee, chocolate, and citrus) and flavor oils (peppermint, cinnamon, and nutmeg) are frequently used. Additionally, flavors may be chosen from oleo resins, artificial flavor oils, and extracts made from different plant components, such as fruits, flowers, etc.[19]

5. APPROACHES USED FOR FORMULATION OF FAST DISSOLVING FILM

For the formulation of a fast-dissolving film, utilize the following technique:

- Solvent casting method
- Semi solid casting method
- Solid dispersion extrusion
- Hot melt extrusion
- Rolling method.[20]

5.1 Solvent Casting Method

In this method, the polymers soluble in water are first dissolved in water at a rate of 1,000 rpm and each & every additional excipient—colors, flavoring, sweetener, etc is dissolved separately. After that, the two solutions are well combined while being stirred 1,000 revolutions per minute. The outcome is combined with the API that has been dissolved in an appropriate solvent. By using a vacuum, the trapped air is released. After the resultant solution is dried and molded into a film, The necessary size pieces are cut out of it.[21]

5.1.1 Advantages of solvent casting

- Excellent homogeneity of thickness
- Superior clarity to extrusion
- Greater adaptability improved physical characteristics
- Typically, the finished film thickness is 12-100um

5.2 Semi Solid Casting Method

This method is usually employed when an acid-insoluble polymer is utilized as a component in a film. Firstly, water is used to dissolve the water-soluble polymers. The resulting solution is mixed with the separately generated acid-insoluble polymer solution. The two solutions are correctly combined. After the two solutions are mixed, the appropriate amount plasticizer is introduced into theresulting final solution to obtain the gel's mass. Finally, Onto the films or ribbon, the gel mass is casts using heat-controlled drums. The ideal thickness for the film is From 0.015-0.05 inches. The acid insoluble polymer and film-forming polymer should have a 1:4 ratio. Cellulose acetate butyrate and cellulose acetate phthalate are two examples of polymers that are insoluble in acid.

5.3 Solid Dispersion

To load the drug, it must be evenly distributed throughout a solution of melting polymer. The medication is mixed with a suitable liquid solvent to create a solid dispersion.which is then added to an appropriate polymer melt that can be cooled to below 70°C without the liquid solvent having to be drained off. In the end, the solid dispersions are formed into films using dyes.[22]

5.4 Hot Melt Extrusion

Carriers aid in the preparation of the initial mass in the hot melt extrusion process. The medication is combined with carriers to create the first bulk, which is then dried and solidified. Next, granular material that has dried is incorporated into the extruder. The temperature of the four zones on the extruder are 800°C (zone 1), 1150°C (zone 2), Zone 3 is 1000°C, and Zone 4 is 650°C. The extruder screw speed needs to be adjusted to 15 rpm in order to process the granules inside the extruder barrel for approximately 3-5 minutes and guarantee that the mass is completely melted. The extruder (T = 650°C) is then pushed into a cylindrical calendar to form a film. Hot melt extrusion apparatus shown in figure-3

5.4.1 Benefits of hot melt extrusion:

- Reduced number of operating units
- Less product waste, potential for expansion
- An anhydrous procedure, lack of organic solvents
- Shorter drug carrier mix residence time & temperature and improved content homogeneity.[23]

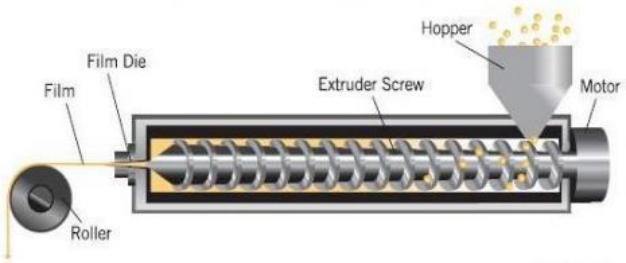

Figure 3 – Hot melt extrusion

5.5 Rolling Method

In the rolling process, a medication suspension or solution including a film-forming polymer is made and then applied to the roller. Particular rheological considerations should be made for the suspension or solution. The primary solvents are water and alcohol-water mixtures. After being dried on the rollers, the film is divided into the appropriate sizes and shapes.[24]

6. FAST DISSOLVING FILM EVALUATION

6.1 Organoleptic and Morphological Regulation

The mouth dissolving film's color, homogeneity, transparency, fragrance, and texture are assessed both viscerally and visually. It is important to assess them specifically in terms of flavor attributes and taste.[25]

6.2 Moisture Absorption Capacity

In order to control the films' physical integrity and stability, this test is conducted in an environment with elevated humidity. Following individual sample weighing, After placing the samples in desiccators filled with a solution of aluminum chloride, they are left to soak up moisture for three days. Following that, the films are measured, and the following formula is used to determine their percentage moisture absorption capacity.[26]

% Capabilities for absorbing moisture =

(Starting Weight – Ending Weight) Starting Mass × 100

6.3 Folding Endurance

A thin film can be repeatedly folded at the same spot until it breaks as a test of its flexibility. The quantity of folds made before breaking is noted. A film is deemed to have exceptional flexibility if it can fold at least 300 times.[27]

6.4 Film Thickness

The thickness of the film is measured with a micrometer screw gauge. Five locations on the film need to be measured: the computed mean thickness, four corners, and the center. It is recommended to test six films of each composition, the maximum thickness variation should be less than 5%, and the mean ±S.D. should be computed. The films have a maximum thickness of less than 5%.

6.5 *In-Vitro* Disintegration Time

To find out, gently shake a beaker containing 10 ml of water after dipping the film in it. Take note of the time after the film dissolves. The point at which the film started to break or crumble was called the *in-vitro* disintegration time. That was done three times.[28]

6.6 Drug Content

Cut to 2 cm² in size, the film is placed in a solvent-filled volumetric flask. After being shaken for two hours in a mechanical shaker to obtain a homogenous solution, this is filtered. After the proper dilution, a UV spectrophotometer is used to identify the drug content.[23]

6.7 Tensile Strength

Tensile strength is the maximum tensile force applied prior to the thin-film specimen breaking. It is computed by dividing the applied force by the cross-sectional area of the film, then multiplying the result by 100.[29]

Tensile Strength = (Load at Failure) / (Thickness of Film × Width of film) × 100

6.8 Weight variation

Using an analytical balance, oral fast-dissolving films were weighed so that an average weight could be determine for each film. It is preferable if the weight of films is almost consistent. ensuring that a film contains the appropriate amount of API and excipients.

6.9 *In-Vitro* drug Dissolution

The (USP) basket apparatus was used to conduct the *in-vitro* dissolution investigation in 500 ml of phosphate buffer pH 6.8 at 37 ±0.5C and 50 rpm. Every square cut film sample

(measuring 2 cm by 2 cm) was immersed in the dissolving media, and at intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 minutes, the proper aliquots were removed and replaced with the same volume of dissolving fluid. Using a model UV-1800 UV-Visible spectrophotometer from Shimadzu, Japan, the samples were filtered with what man filter paper for each batch before being subjected to spectrophotometric analysis at particular lambda max. Sink conditions were kept constant during the trial.[30]

6.10 Stability Study

In the humidity chamber, an accelerated environment with 65% relative humidity and 35°C temperature is used to conduct the stability investigation. After three months, the drug content, disintegration time, and physical appearance of films are evaluated.

7. MARKETED ORAL FILM PRODUCT

The list of marketed products with the use & name of the manufacturing company are given in table-4.

Table 4- List of available marketed items of fast dissolving film

Product	API	Manufacturer	Use
Listerine	Cool mint	Pfizer,lnc.	Mouth ulcer
Benadryl	Diphenhydramine HCL	Pfizer	Anti allergic
Suppress	Menthol	Innozen,lnc.	Cough suppressant
Klonopin wafers	Clonazepam	Solvay pharmaceutical	Anti anxiety
Theraflu	Dextormethorphan	Novartis	Anti allergic
Orajel	Menthol/pectin	Del	Mouth freshner
Gas-x	Simethicone	Novartis	Anti flatuating
Chloraseptic	Benzocain/menthol	Prestige	Sore throat
Sudafed PE	Phenylepinephrine	Wolters lkuwer Health	Congestion
Triaminic	Diphenhydramine	Novartis	Anti allergic

8. DIFFICULTIES IN FORMULATING AND DEVELOPING QUICK-DISSOLVING FILM

There is prosperity of literature accessible today regarding the development, formulation, and assessment of oral fast-dissolving or fast-disintegrating tablets and films. Nevertheless, the formulator has several difficulties when creating these dosage forms. It's essential to solve these issues since they could aid in future study exploration of the specific field and potentially aid in overall creation and arrangement. Patient compliance has a direct bearing on these difficulties. They should so be given top priority during the formulation and development stages.

Here are a few of the challenges in creating an oral film. These include:

- Insolubility of drug
- A shorter time for the film to dry
- High dose incorporation in film
- Co administration of drug
- The resistance of the film to temperature and humidity
- Need special packaging
- Dose uniformity

9. CONCLUSION

Fast dissolving films provide a rapid onset of action and improved patient compliance, as this review shows, making them a viable dosage form. Fast-dissolving films are used for patients with swallowing difficulties, as well as for the elderly and pediatric populations. In comparison to the other dosage form, it also has a lot of benefits, such as improved dissolution, disintegration, bioavailability over existing dosage form. In addition film avoid first pass metabolism due to pregastric absorption. They are a viable option for the oral route. Owing to these benefits, mouth dissolving film was able to treat patients effectively.

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