

A REVIEW OF THE ORAL FILM IS A NOVEL APPROACH TO ORAL DRUG DELIVERY SYSTEM

**Dr. Abhinav .P. Mehta¹, Mr. Kalpesh Suresh Patil², Miss. Ujwala Prakash Chaudhari³,
Mr. Sagar Subhash Kothari⁴**

RCPIPER Shirpur, Dist Dhule, 425405 Maharashtra, India

Abstract

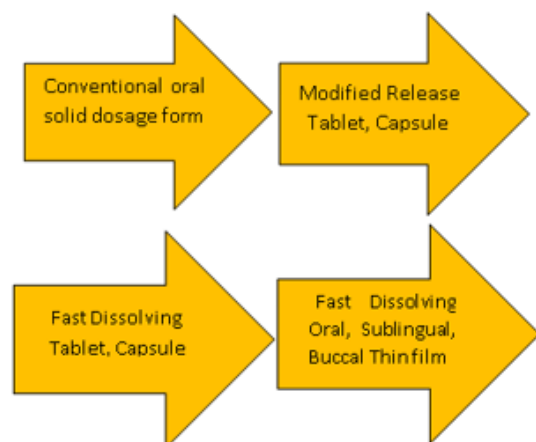
For geriatric and pediatric patients who have difficulty swallowing, a quick disintegrating drug delivery system was created in the late 1970s as an alternative to capsules, tablets, and syrups. Several orally disintegrating pills were developed to meet the need, which disintegrates in the mouth in one minute without chewing or drinking water. Later, oral drug delivery technology advanced from conventional to modified release dosage forms, and rapid disintegrating films, rather than oral disintegrating tablets, was produced recently. The films are designed to dissolve in a few seconds when they come into touch with a wet surface, such as the tongue, allowing the user to ingest the product without needing any additional liquid or water. This ease of use has both a marketing and a compliance benefit for patients. The drug avoids gastrointestinal degradation and the first-pass effect because it is absorbed directly into the systemic circulation. These films are constructed comprised of thin oral strips made of hydrophilic polymers that break down and dissolve quickly when put in the mouth, releasing the medicine for Oro mucosal absorption without chewing or drinking water. The oral film dosage form minimizes adverse/side effects while also being cost-effective. The structure of the oral mucosa and the basic circumstances of mucosal adhesion are discussed in this article. For the formulation of oral dissolving films, a variety of processes are available, with the solvent casting method being the most popular.

Keyword: Rapid disintegrating film, oral strip, Pediatric, Geriatric, first-pass effect

1.INTRODUCTION

Based on the technology of the transdermal patch, mouth dissolving films, a new drug delivery device for oral medication delivery, have been created. The delivery method consists of a very thin oral strip that is applied to the patient's tongue or any other oral mucosal tissue. When the film is wet by saliva, it quickly hydrates and binds to the application site.[1] It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allowing for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets.[2] The large surface area of the film, which wets quickly when exposed to the environment, contributes to the fast-dissolving activity. For the increased bioavailability, fast-dissolving drug delivery systems are specifically designed for potent (low dose) drugs and drugs exhibiting rapid first-pass effect.[3] Because of its simplicity and ease, the oral route remains the most preferred route, with significantly enhanced patient compliance.[4] The introduction of Oral Dissolving Tablet (ODT) to the market was accompanied by public education about how to correctly utilize the medicine, including instructions like "do not swallow" or "do not chew." It was also necessary to manipulate the ODT in the oral or buccal cavity. However, because Oral Strip Technology (OST) derived products were already widely available in the market as breath-freshening strips, there was no need to re-educate the public on how to use this dosage form. OST was already popular among the general

population in the early 2000s, thanks to the introduction and widespread use of Listerine pocket strips, a mouthwash innovation.[5]



1.1 Advantages of oral films drug delivery system:[6] [7]

1. They come in a variety of sizes and shapes.
2. Mucoadhesion is quite good.
3. Rapid release and breakdown in the mouth within minutes.
4. Water does not necessitate swallowing.
5. It is slim and graceful.
6. It works well with flavor masking.
7. It leaves a small amount of residue in the mouth if any at all.
8. It's useful in situations where quick response is necessary, such as abrupt allergic reactions or coughing, motion sickness, bronchitis, or asthma.
9. The quick breakdown and dissolving of these tablets increase bioavailability, especially for insoluble and hydrophobic medicines.
10. Patient compliance has improved.

1.2 Disadvantages of oral films drug delivery system[8]

1. Dose homogeneity is a technological hurdle to overcome.
2. Hygroscopic in nature
3. High doses cannot be incorporated
4. Specific packaging is required for product stability and safety

2. ANATOMY AND PHYSIOLOGY OF THE ORAL MUCOSA

The stratified squamous epithelium on the surface, the basement membrane on the inside, and the connective tissue of the lamina propria and submucosa on the outside make up the oral mucosa. The permeability of the buccal mucosa is 4–4000 times that of the epidermis of the skin and less than that of the intestinal mucosa.[9] Sublingual > buccal > palatal is the sequence of permeability in the oral cavity. This is because the two tissues are anatomically different: sublingual tissue is thin and nonkeratinized, whereas palatal tissue is keratinized. The permeability barriers of the oral mucosa are described below. [10]

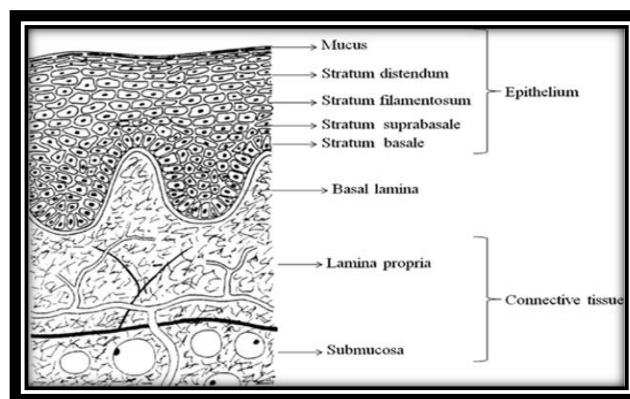


Fig-01 Cross-section of the oral mucosa [11]

The major purpose of (Oral Cavity) OC, which has a surface area of about 200 cm², is to protect the underlying tissue from mechanical and chemical harm as well as foreign substance invasion. The oral mucosa is made up of three types of mucous membranes: masticatory mucosa, specialized mucosa, and lining mucosa. [12] This diagram depicts the distribution of this mucosa along with the OC. According to Collins and

Dawes, the masticatory mucosa, lining mucosa, and specialized mucosa account for 25%, 60%, and 15% of the total surface area of the oral mucosa, respectively. The OC's chemical resistance and mechanical strength are provided by the masticatory mucosa, which includes the gingiva and hard palate. [12] The four primary layers of this mucosa are keratinized, granular, prickle-cell, and basal. The lining mucosa covers the buccal epithelium, soft palate, sublingual area, and upper and lower lips, giving the OC flexibility. There are four layers to the mucosa: superficial, middle, prickle-cell, and basal. Finally, the dorsal surface of the tongue is defined by specialized mucosa.[13]

2.1 Physiological functions of saliva: [14]

1. Oral mucosa modulation
2. Calcium phosphate salts for tooth remineralization

3. Acid neutralization in the mouth.
4. Epithelial proliferative stimulation Digestion of fat and carbohydrates begins.
5. Oral, pharyngeal, and esophageal mucosa lubrication and washing.

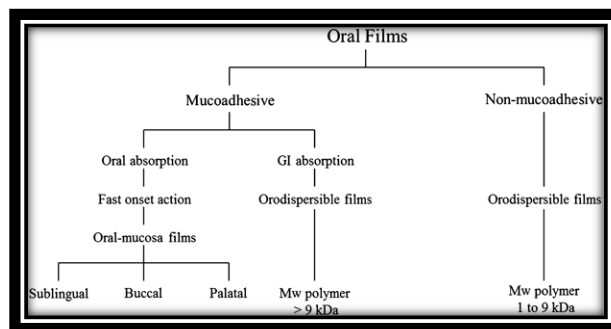


Fig-02 Classification of oral film

Table 1. A typical composition of the oral film [7]

Sr.no	INGREDIENTS	AMOUNT (w/w)
1	Active Pharmaceutical Ingredient	1-25%
2	Film Forming Polymer	40-50%
3	Plasticizer	0-20%
4	Saliva Stimulating Agent	2-6%
5	Sweetening agent	3-6%
6	Flavoring agent	QS
7	Coloring agent	QS

a. Active Pharmaceutical Ingredient:-

By weight, a typical film contains 1-30% active medicinal component. Because it improves the texture of the film and enables rapid dissolution and homogeneity in the fast dissolving film, micronized API is essential for effective formulation. Pediatrics (antitussives, expectorants, anti-asthmatics), geriatrics (antiepileptics, expectorants), gastrointestinal diseases, nausea (e.g. due to cytostatic therapy), pain (e.g. migraine), and the central nervous system (e.g. Anti Parkinsonism therapy) are all examples of drugs that can be formulated as mouth dissolving films.[15]

b. Film Forming Polymers:-

The most significant component of the oral quick-dissolving film is polymers. The amount of polymer supplied to the oral strip determines the film's toughness. The medical and nutraceutical industries have been particularly interested in these polymers. In most cases, 45 % w/w polymer is employed, based on the total weight of the dry film. The oral strip is mostly made of hydrophilic polymers, which degrade quickly in the mouth when they come into contact with saliva.[16]

Table 2. Polymers used in the formulation fast dissolving film[7]

Polymer	Examples
Natural polymer	Pullulan, starch, gelatin, pectin, sodium alginate, maltodextrins, polymerized rosin
Synthetic polymer	Hydroxypropyl methylcellulose, sodium carboxymethylcellulose, polyethylene oxide, hydroxypropyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, ethyl cellulose

c. Plasticizers: - Film mechanical properties have been observed to be influenced by formulation concerns (plasticizer, etc.). The use of plasticizers increased the mechanical properties of the films, such as tensile strength and elongation. These properties may be affected by changes in their concentration. Glycerol, dibutylphthalate, and polyethylene glycols are some of the most regularly used plasticizers.[17]

d. Saliva Stimulating Agent:- Faster disintegration of rapid dissolving film compositions is aided by increased saliva production. As a result, the formulations should include acids that are commonly utilized as salivary stimulants in food preparation. Salivary stimulants include citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid, with citric acid being the most popular.[18]

e. Flavoring Agent:- Flavoring agents include synthetic flavor oils, oleoresins, and extracts derived from various parts of plants, such as leaves, fruits, and flowers. Flavors can be used singly or in groups. Menthol essential oils or water-soluble extracts, strong mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavors such as lemon, orange, or sweet confectionery flavors such as vanillin, chocolate, or fruit essences such as apple, raspberry, cherry, and pineapple can all be used. The type of flavor and its strength dictate the amount of flavor required to mask the taste.[19]

f. Sweetening Agent:- Sweeteners have become a common component of oral drugs that dissolve or disintegrate. Sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose are the most prevalent sweeteners. Polyhydric alcohols with a pleasant

mouthfeel and a cooling effect, such as sorbitol, mannitol, and isomalt, can be blended. Saccharin,

cyclamate, and aspartame are examples of first-generation artificial sweeteners, while acesulfame-k, sucralose, alitame, and neotame are examples of second-generation artificial sweeteners. Sweeteners are widely employed in concentrations of 3 to 6% w/w, either alone or in combination.[9]

g. Colouring Agent:- When some of the formulation ingredients or medications are present in insoluble or suspension form, pigments such as titanium dioxide or FD&C approved coloring additives are added (not more than 1% w/w) in OS.[20]

3. APPROACHES USED FOR THE FORMULATION OF FAST DISSOLVING FILMS

Conventional approaches :-

3.1 Solvent Casting Method: [21]

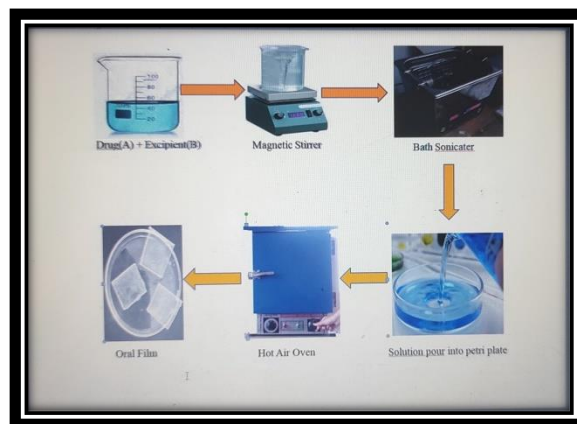


Fig-03 Solvent Casting Method

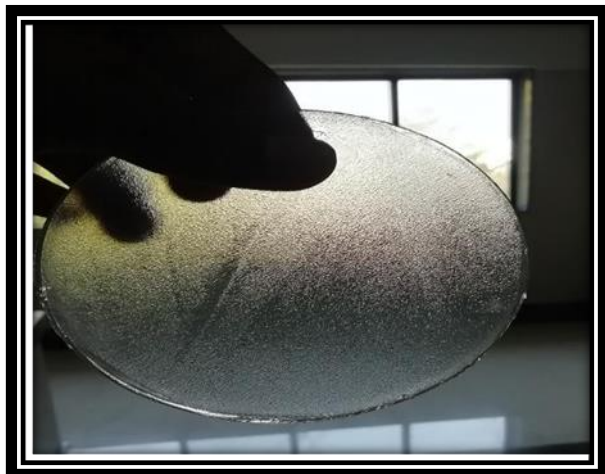


Fig-04 Prepared Oral film

The polymeric solution (Solution A) was made by dissolving the necessary amount of polymer in distilled water (70 %). With constant stirring, a specific amount of medication, plasticizer, and other excipients were dissolved in the remaining water (30%). (Solution B). With constant stirring, solution B was gently added to polymeric solution A. For defoaming, the final solution was set aside for 30 minutes. After defoaming, the Petri plate was lubricated with Plasticizer and the final solution was poured in Petri plate and dried at 45 °C in a hot air oven for 24 h. Film cast in Petri plate was then carefully peeled off and cut into pieces of desired shape and size.

3.2 Semi-solid casting

A solution of water-soluble film-forming polymer is mixed with a solution of acid-insoluble polymer to generate a homogeneous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate). After sonication, it is coated on untreated casting film. After drying, the film thickness should be between 0.015 and 0.05 inches. In a 1:4 ratio with the film-forming polymer, the acid-insoluble polymer should be used.[17]

3.3 Hot-Melt Extrusion method:

The plasticizer is progressively introduced after the drug and polymers have been combined for 10 minutes in a sigma blade mixer. In the presence of an anti-sticking agent, the mixture is granulated. Granules are held at

room temperature overnight before being sieved using a 250m sieve to remove surplus powder and standardize particle size. The extruder receives the dried granular material. The films are cut to the size required for testing and individually packed in airtight packages after the preparation processes.[22]

3.4 Rolling method:

The rolling process involves the production of a premix, the addition of active, and then the formation of the film. Except for the API delivered to the masterbatch feed tank, the pre-mix batch contains film-forming polymer, polar solvent, and other components. The first metering pump and control valve then feed a predefined amount of the masterbatch. The necessary amount of medicine is added to the mixer, and the mixture is mixed for long enough to generate a homogenized matrix. The second metering pump feeds a predetermined amount of matrix into the pan. The film thickness was determined by the metering roller. Finally, the film is created on the substrate and transported away by the support roller. Controlled bottom drying is used to dry the damp.[23]

4. EVALUATION ORAL FILM

4.1 Visual inspection:

Visual observation was used to assess the appearance of rapid dissolving films, such as the strip's transparency and semitransparency. [24]

4.2 pH Value:

By dissolving one oral film in 10ml distilled water and measuring the pH of the resulting solution, the pH value can be determined. The film needs to have an almost consistent pH value. [25]

4.3 Thickness:

The film thickness is a critical determinant of formulation component distribution uniformity. At various points on the film, the thickness was measured using a digital Vernier Calliper with a least count of 0.01 mm. [26] The thickness of the film was measured at three distinct

locations on the film, with an average and SD determined. [27]

4.4 Folding endurance:

For the prepared films, the folding endurance was carefully measured. A strip of film was cut and folded over and over again until it broke. [28] The value of folding endurance was determined by the number of times the film could be folded in the same location without breaking.[29]

4.5 Weight Variation:

Different batches of the formulations were sliced into 4 cm² films, and weights were recorded on an electronic balance. Three films were chosen at random for each formulation.[30] For the weight variation test, ten films from each batch were individually weighed on a digital electronic balance and the average weight was computed. [31]

4.6 Tensile strength:

The greatest stress applied to a point where the strip specimen breaks are known as tensile strength.

[29] It is computed by dividing the applied load at rupture by the strip's cross-sectional area, as shown in the equation below. [32]

Tensile strength = Load at breakage / Strip thickness × Strip width

4.7 Percentage moisture loss:

A % moisture loss test was performed to verify the film's integrity and physical stability. [33] A film with a surface area of 2×2 cm² was cut and weighed. After that, the film was placed in a desiccator with fused anhydrous calcium chloride for three days. After three days, the film patch was removed and weighed once more. The following calculation was used to compute the % moisture loss of the film. [21]

Percentage Moisture Loss = (Initial Weight - final weight)/Initial Weight × 100

4.8 Drug content:

The UV Spectrophotometric technique was used to determine the drug content of all films. This was accomplished by cutting a 2x2cm² film and dissolving it in 100ml of 6.8 phosphate buffer solution. Whatman Filter paper was used to filter the solution, and a UV-Spectrophotometer was used to measure the absorbance.[1] When it came to drug content, the pictures were approved when the range was between 85 and 115 %. The average of three readings was used to determine the drug content. [34]

4.9 Disintegration test:

The CDER guidance's 30 second or shorter disintegration time requirement for orally disintegrating tablets can be applied to fast dissolving oral strips. Although there is no formal recommendation for oral rapid dissolving films/strips, this can be used as a qualitative guideline for quality control tests or during the development stage. [35]A petri dish was filled with 10 ml of pH 6.8 phosphate buffer, and the film was placed on top of it. Shake the Petri plate every 10 seconds. [36] The length of time it took for the film to disintegrate was recorded. [37]

4.10 In vitro Dissolution studies:

The dissolving of films was investigated in 900 ml of pH 6.8 buffer using a USP dissolution test 2 device with a paddle stirrer spinning at 50 rpm. Throughout the experiment, a temperature of 37 °C ± 10 °C was maintained. Raw material disseminated in the dissolving liquid was used to adhere the films to the central shaft. 5 mL samples were withdrawn through a filter at various time intervals (0, 10, 20, 30, 40, 50, 60, and 90 minutes). [34],[1]To maintain constant volume and sink conditions, an identical volume of dissolving medium was added after each sample extraction. UV analysis was used to determine the amount of medication that had been released. The percentage of medication released against time was plotted.[37][39]

4.11 Ex vivo Permeation Study:

Ex vivo experiments on swine sublingual tissue were conducted using the DBK Franz diffusion cell. Sublingual

tissue was placed between the donor and receptor compartments. To maintain hydrodynamics, the receptor compartment was filled with pH 6.8 phosphate buffer that was held at 37.0°C with a magnetic stirrer. The film was inserted in the donor compartment, which was filled with 1 mL of phosphate buffer pH 6.8. Samples were taken at predetermined intervals. [40] The amount of medication penetrated per square centimeter was determined by measuring the absorbances with a UV visible spectrophotometer. A comparable study was carried out with 1 mg of the drug. Both the video and the drug had their flux estimated. [33]

4.12 Stability studies:

The oral film samples should be stored at 40±0.5°C and 75±5%RH for three months in order to undertake stability studies according to ICH recommendations. [41][19] At 0, 30, 60, 90, and 180 days, the samples were taken out and examined for drug content.[39]

5. CONCLUSION:

In today's environment, it's critical for formulators to give both uniqueness and consumer happiness at the same time. As a result, oral dissolving films have been identified as a viable and unique technique for optimizing drug therapeutic effect while also improving patient compliance. It has been discovered to be more beneficial than traditional dosage forms. Because of the availability of innovative technology, as well as high market acceptance and patient demand, the future potential for quick dissolving dosage forms is bright. Future advancements in quick dissolving drug delivery systems are promising, although the technology is still in its infancy, and development is ongoing. To properly utilize this technology, more items must be commercialized. The current study shows that a fast-dissolving oral film is the most acceptable and precise oral dosage form since it bypasses the hepatic system and provides a better therapeutic response.

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