



A Review on the Fast Dissolving Sublingual Film

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Abstract: - Oral fast dissolving films are an advanced technique that has a quick onset of action and improves patient compliance. Many patients, particularly pediatric and geriatric patients, have difficulties swallowing tablets and hard gelatin capsules and do not take their medications as prescribed. Approximately 35% of the general population suffers from swallowing difficulties or dysphasia. It enhances the efficacy of APIs and promotes medication use. These formulations are effective for colds, allergic rhinitis, asthma attacks, and CNS problems that require rapid onset of action for faster relief. The sublingual path of drug administration is very effective because the drug is absorbed through the sublingual blood vessels without passing through the hepatic first pass metabolism, resulting in improved bioavailability. The current article provides a summary of the formulation aspects, manufacturing methods such as solvent casting, assessment parameters, and sublingual uses of fast dissolving films.

Keywords: Fast dissolving sublingual film, disintegration time, film-casting, oral films, the onset of action.

Introduction

Fast Dissolving Drug Delivery Systems has a number of advantages over traditional dose forms since the drug dissolves in the saliva without the need for water. Fast Dissolving Drug Delivery Systems is an innovation that competes with the existing oral drug delivery systems including tablets, syrups, and capsules. It was created in the early 1970s¹. Tablets and capsules are the most often used oral solid dose forms. Many patients, especially young children and the elderly find it difficult to swallow tablets and hard gelatin capsules and do not take their medications as directed. Approximately 35% of the general population is estimated to have difficulty swallowing, often known as dysphagia². The taking of tablets or capsules may become challenging in particular situations, such as motion sickness, abrupt episodes of allergic attack or coughing, fear of

choking, and a lack of water. Several quick-dissolving medication delivery devices have been created to get around these issues³. Sublingual administration of the medication entails placing the medication beneath the tongue, where it is then directly absorbed into the bloodstream between the tongue's ventral surface and the floor of the mouth. The internal jugular veins, facial veins, and brachiocephalic veins all play a role in the quick absorption of the medication solutes into the reticulated vein, which is located beneath the mouth mucosa. Only a hypodermic injection can reduce the absorption through the sublingual route, which is 3 to 10 times higher than the oral route⁴. It can be used to replace the fast dissolving tablet's shortcomings⁵. Fast dissolving films resemble ultra-thin postage stamp strips in terms of their size, shape, and thickness. Easily to place the fast-dissolving film on the patient's tongue or any other oral mucosal tissue. When saliva immediately moistens the film, it quickly hydrates and sticks to the application site. The drug is then quickly released and disintegrates, allowing for oromucosal absorption. This fast-dissolving drug delivery system (FDDS) is used to increase bioavailability while lowering dosage frequency to approach plasma peak levels, which reduces side effects and increases cost-effectiveness. It is suitable for medicines with high first pass metabolism⁶.

Drug distribution via oral administration causes issues with hepatic first pass metabolism and GI tract enzymatic degradation. These issues can be resolved for a certain class of drug by administering them through the sublingual mucosa⁷.

Overview of the oral cavity⁸

To comprehend the environment offered for medication delivery, the structure and anatomy of the mouth cavity are explored [Fig. 1]. The outermost layer of the oral mucosa is made up of stratified squamous epithelium. A basement membrane, lamina propria, and submucosa make up the layers underneath this one. In terms of permeability, the oral mucosa falls somewhere in the middle between the epidermis and the intestinal mucosa. The buccal mucosa's permeability is thought to be 4–4000 times greater than the skin. Because different oral mucosa has different structures and functions, there are significant differences in permeability between different areas of the oral cavity. The oral mucosa prevents first pass metabolism and permits direct medication entry into the systemic circulation.

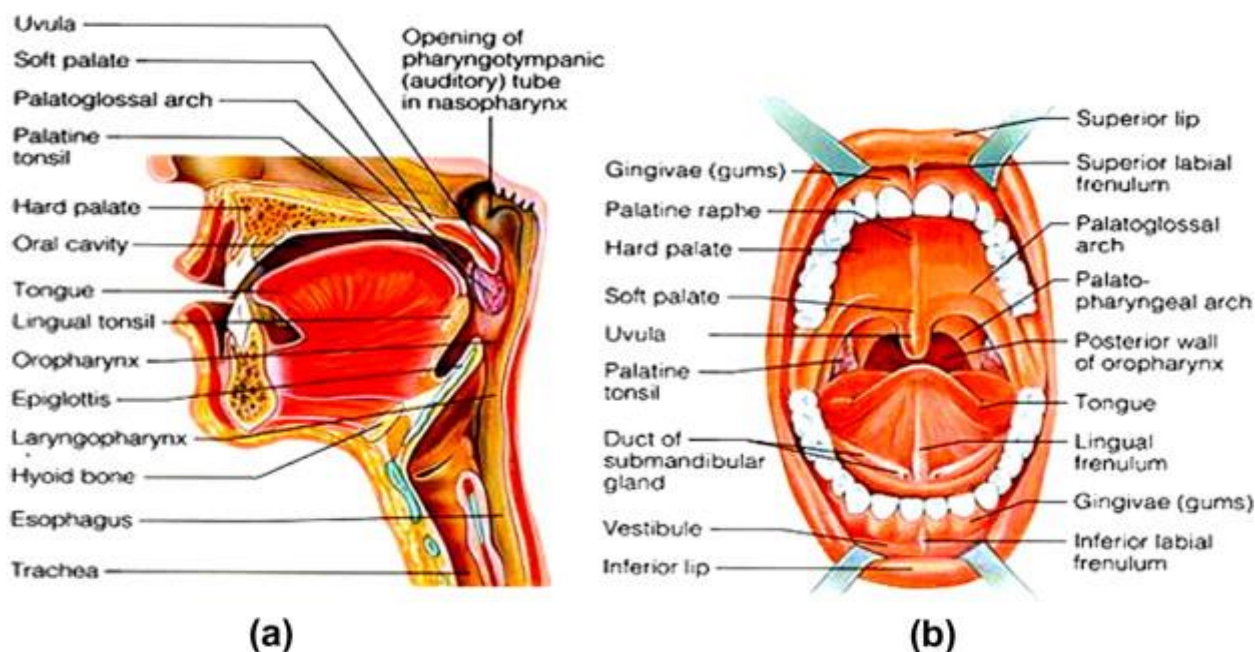


Figure: Overview of the oral cavity

Sublingual gland^{9,10}

Under the tongue, on the floor of the mouth, are salivary glands. They are also referred to as sublingual glands. They create mucin, which then creates saliva. Food is mixed with gland-produced fluid, making it easier to chew. It is possible to say that absorption is directly inversely related to layer thickness since absorption is the process by which a drug is transferred from the site of delivery into the systemic circulation. The absorption of the drug follows in this way Sublingual > Buccal > Gingival > Palatal. The sublingual route can induce a rapid beginning of effect due to strong permeability and a rich blood supply, allowing the delivery of drugs with short half-lives and frequent dosing schedules.

Permeability¹¹

The intestinal mucosa and the epidermis are both relatively leaky epithelia, as is the mouth mucosa. The permeability is thought to be 4-4000 times greater than the skin. The buccal mucosa is thicker and nonkeratinized, but the sublingual mucosa is comparatively thin and keratinized. As a result, the buccal mucosa's permeability decreases in the order of sublingual greater than buccal and the degree of keratinization of these tissues.

Mechanism of absorption¹²

Drug solutes administered sublingually are quickly absorbed into the reticulated vein, which is located beneath the mouth mucosa. From there, they travel through the internal jugular vein, brachiocephalic vein, facial vein, and reticulated vein before being emptied into the systemic circulation. Drugs administered sublingually enter the bloodstream through the tongue's ventral surface and the floor of the mouth. Sublingual medication absorption is 3 to 10 times greater than oral absorption and is only surpassed by hypodermic injection.

Factors affecting absorption¹³

- Solubility in salivary secretion in addition to high lipid solubility, the medicine should be soluble in aqueous buccal fluids, implying that biphasic solubility is required for absorption.
- Binding to the oral mucosa drugs that bind to the mouth mucosa has low systemic availability.
- Saliva's pH and pKa values the average pH of saliva is 6.0, which enhances the absorption of medicines that are still in their unionized state. Additionally, if the pKa is higher than 2 for an acid and lower than 10 for a base, the medications are absorbed via the mouth mucosa.
- The thickness of the oral epithelium as opposed to buccal thickness, the sublingual epithelium is thinner, measuring 100–200 m. As a result of the thinner epithelium and the drug's immersion in less saliva, the absorption of medicines is accelerated.
- A drug's lipid solubility must be slightly higher for passive permeation than for GI absorption in order for the drug to be entirely absorbed through the sublingual route.
- Lipophilicity of the drug.

Advantages of film^{14,15}

- Ease of administration for patients, such as young children, elderly people, and people with mental illnesses, who are unable to swallow a tablet.
- This route of administration makes it comfortable to provide medications and allows for more exact dosing in comparison to liquid doses forms.
- The absence of water required to utilize this dose form is advantageous for persons who are traveling and have limited access to water.
- This mode of administration greatly reduces the effects of first-pass metabolism.
- The film dissolves considerably more easily than other solid dose forms.
- It also eliminates the risks and inconveniences associated with intravenous therapy.
- Access to a wider surface area leads to rapid disintegration and dissolution in the oral cavity within seconds.
- Some medications are absorbed from the mouth, pharynx, and esophagus as saliva flows down into the stomach, increasing drug bioavailability.

Disadvantage of film¹⁵

This site is not well adapted to long-term distribution methods.

Sublingual medicine cannot be administered when a patient is asleep or unwilling to cooperate.

The patient should not smoke while using sublingual medicine since smoking induces vasoconstriction of the blood vessels. This will reduce the effectiveness of the drug.

Ideal characteristics of the drug to be selected¹⁶

The drug should have a pleasing taste.

The drug to be incorporated should have a low dose upto 40mg.

At the pH of the oral cavity, it should be partially unionized.

It should be able to penetrate the oral mucosal tissue.

Smaller and more moderate molecular weight drugs are preferred.

Formulation of fast dissolving films^{17,18,19}

A mouth dissolving film is a thin film with an active component that has a surface area of 5-20 cm². The quick dissolving in water or saliva is achieved using a unique matrix made of water-soluble polymers. A typical composition contains the following:

Table 1: Composition of fast dissolving films

Sr. No	Composition of film	Quantity
1.	Active pharmaceutical agent	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	10%
7.	Coloring agent	1%

1. Active pharmaceutical agent

The drugs chosen for oral films should be stable in saliva and water at low doses. The drug should be present in the film at a concentration of 1 to 25% w/w. small dosage molecules are the most likely ones for incorporation into an oral fast dissolving film. Multivitamins up to 10% w/w of dry film weight were integrated into the films with a dissolving period of less than 60 seconds. Micronized API is always beneficial for enhancing the texture of the film as well as for better dissolution and uniformity in the Oral fast dissolving film.

Table 2: Drugs that can be incorporated into fast dissolving film

Active pharmaceutical category	Therapeutic category	Dose
Nicotine	Smoking cessation	1-15mg
Zolmitriptan	Anti migraine	2.5mg
Loratidine	Anti histaminic	5-10mg
Omeprazole	Proton pump inhibitor	10-20mg
Ketoprofen	Anti inflammatory	12.5-25mg
Oxycodone	Opoid analgesic	2.5-10mg
Dicyclomine	Muscle relaxants	25mg
Nitroglycerin derivatives	Vasodilator	0.3-0.6mg

2. Film forming polymer

There are many types of polymers available for the perpetration of fast dissolving film. The films obtained should be strong enough to withstand handling and transit without harm. The strip's toughness is determined by the type of polymer used and the amount used in the formulation. To get the desired strip qualities, the polymers can be used alone or in combination. Water-soluble polymers are utilized as film formers. The water-soluble polymers give the films quick disintegration, a pleasing mouth feel, and mechanical qualities. By increasing the molecular weight of the polymer film basis, the disintegration rate of the polymers is slowed. Natural and synthetic polymers can both be employed in the formulation of sublingual films. Excipients or polymers must be water soluble with low molecular weight and excellent film forming capacity in order to make a water-soluble film formulation. In general, at least 45% w/w polymer should be present depending on the total weight of the dry film. Usually, the 60-65% w/w polymer is often selected to get desirable characteristics. The polymer used should be non-toxic, irritant-free, and free of leachable contaminants. It should have good wetting and spreading capacity. The polymer should have enough peel, shear, and tensile strength. To make fast dissolving films, natural and synthetic polymers such as cellulose or cellulose derivatives, pullulan, gelatin, Hypromellose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, xanthan gum, tragacanth gum, and guar gum are used. Pullulan is a nonanimal-derived natural polymer that does not require chemical treatment.

3. Plasticizers

It helps in the improvement of the strip's elasticity and decreases its brittleness. Plasticizer dramatically enhances strip characteristics by lowering the polymer's glass transition temperature. Some commonly used plasticizer excipients are glycerol, propylene glycol, low molecular weight propylene glycols, phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin, and castor oil. Plasticizers are typically employed in concentrations ranging from 0 to 20% w/w of the dry polymer weight.

4. Saliva stimulating agent

The use of saliva stimulating substances is aimed at increasing the rate of saliva production, which will aid in the faster disintegration of the rapid dissolving strip formulations. These ingredients are employed alone or in combination in amounts ranging from 2-6% w/w of the strip. Salivary stimulants include citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid.

5. Sweetening agent

Sweeteners have become an essential component of pharmaceutical products designed to be disintegrated or dissolved in the oral cavity. Sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose are the most common sweetener sources. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be combined because they produce a nice mouthfeel and a cooling effect. Saccharin, cyclamate, and aspartame are examples of first generation artificial sweeteners, followed by acesulfame-k, sucralose, alitame, and neotame, which are examples of second generation artificial sweeteners. Sweeteners are commonly employed in concentrations ranging from 3 to 6%w/w, either alone or in combination.

6. Flavoring agent

Fast dissolving film compositions should contain up to 10%w/w flavors. An individual's approval of an oral disintegrating or dissolving formulation is mostly determined by the initial flavor quality observed in the first few seconds after the product has been consumed, as well as the aftertaste of the formulation, which lasts for at least 10 minutes. The elderly prefers mint or orange flavors, whilst the younger generation prefers fruit punch, raspberry, and so on. Flavoring agents can be chosen from synthetic flavor oils, oleo resins, and extracts produced from various plant components such as leaves, fruits, and flowers. Oil or water-soluble extracts of menthol, powerful mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit tastes such as lemon, orange, or sweet confectionery can all be added. Vanillin, chocolate, or fruit essences such as apple, raspberry, cherry, or pineapple.

7. Colouring agent

A wide variety of colours are available, including FD&C colours, EU colours, natural Colouring agents and natural juice concentrates, pigments such as titanium dioxide, silicon dioxide, and zinc oxide, and custom Pantone matched colours.

Manufacturing methods^{20,21}

The following processes can be used to manufacture fast dissolving films:

1. Solvent casting
2. Semi solid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

1. Solvent casting method

In the solvent casting method, water soluble polymers are dissolved in water, and the drug, along with other excipients, is dissolved in a suitable solvent. Both solutions are then mixed and stirred before being casted in a Petri plate, dried, and cut to uniform dimensions.

Londhe V Y and Umalkar K B were prepared fast dissolving film of Telmisartan by using solvent casting method.

2. Semi solid casting

In the semisolid casting method first, a solution of water-soluble film forming polymer is prepared. The obtained solution is mixed with an ammonium or sodium hydroxide solution of an acid insoluble polymer (e.g., cellulose acetate phthalate, cellulose acetate butyrate). A sufficient quantity of plasticizer is then added to form a gel mass. Finally, using heat-controlled drums, the gel mass is cast into the films or ribbons. The film's thickness ranges from 0.015 to 0.05 inches. The acid insoluble polymer to film forming polymer ratio should be 1:4.

3. Hot melt extrusion method

The drug is initially combined with carriers in solid form in the hot melt extrusion process. The mixture is then melted by an extruder equipped with heaters. Finally, the dies form the melt into films.

There are certain benefits of hot melt extrusion.

- Fewer operation units
- Better content uniformity
- An anhydrous process.

4. Solid dispersion extrusion

Immiscible components are extruded with medication in this process, and subsequently, solid dispersions are created. Finally, dies are used to mould the solid dispersions into films.

5. Rolling method

A solution or suspension containing a drug is rolled on a carrier in the rolling method. The solvent is mostly water or a combination of water and alcohol. The film is cured on the rollers before being cut into the desired shapes and sizes.

Evaluation parameter of sublingual film^{22,23,24,25,26}

1. Thickness

The thickness of the film was measured with the help of Vernier Calliper at three different places and the averages of three values can be calculated. This is necessary to ensure uniformity in the thickness of the film, which is directly related to dose accuracy in the film.

2. Weight variation

The cast film was cut into four centimeter squares in three distinct spots. The weight of each film was taken, and the weight variation was determined.

3. pH value

To determine the pH value, dissolve one oral film in 10ml pure water and measure the pH of the resulting solution. It is necessary that the pH of the film be approximately consistent.

4. Folding endurance

Folding endurance was determined by repeatedly folding the film in the same place until the strip broke. The folding endurance value was calculated by counting the number of times the film could be folded without breaking.

5. Content uniformity

To determine the drug content, dissolve the film in 100 ml of an appropriate solution to obtain a 20 g/ml solution. An aliquot of 2ml sample can be removed and diluted to 10ml with a solution.

The solution can then be filtered through a Whatman filter and spectrophotometrically evaluated.

6. Young's modulus

Young's modulus, also known as elastic modulus, is a measure of strip stiffness. It is defined as the applied stress over strain ratio in the region of elastic deformation. Strips that are hard and brittle have a high tensile strength and a young's modulus with a small elongation.

7. In vitro dissolution study

The in vitro dissolution study can be performed in 500 ml of pH 6.8 phosphate buffer using a (USP) XIV paddle apparatus II at 37[±]0.5°C and 50 rpm. Each square cut film sample was immersed in the dissolution media for 30 minutes, with appropriate aliquots collected at prescribed intervals. A UV Spectrophotometer is used to determine the drug concentration.

8. Morphology study

A motic electron photomicrograph can be used to study the morphology of the created film. At 100 X magnification, motic electron photomicrographs can be obtained.

9. Stability study

Stability studies on the prepared formulations of an oral rapid dissolving film are being conducted to investigate the effect of temperature and humidity on the drug's stability. The film can be stored in aluminum foil and subjected to room temperature stability testing. At 90 and 180 days, the sample can be withdrawn and subjected to disintegration tests and in vitro dissolution studies to evaluate disintegration time and cumulative% drug release.

Marketed products^{27,28}

A list of various fast dissolving film marketed formulations is given in table no 3 below.

Table: 3. List of fast dissolving film

S. No.	Brand name	API	Manufacturer
1	Orazel	Menthol/ Pectin	Del
2	Gas-X	Simethicone	Novartis
3	Benadryl	Diphenhydramine HCl	Pfizer
4	Chloraseptic	Benzocaine	Prestige
5	Ondansetron	Ondansetron	Labtech
6	Maxalt MLT	Rizatriptan	Merck
7	Zoming-ZMT	Zolmitriptan	Astra Zeneca
8	Febrectol	Paracetamol	Pyrographer
9	Nimulid	Nimesulide	Panacea Biotech
10	Torrox MT	Rofecoxib	Torrent Pharmaceuticals
11	Romilast	Montelukast	Ranbaxy
12	Nov	Hyoscyamine sulfate	Cyma Labs
13	FazaClo	Clozapine	Azur Pharma
14	Mirtazapine	Mirtazapine	Teva Pharmaceuticals
15	Parcopa	Carbidopa/Levodopa	Schwarz Pharma
16	Theraflu	Dextromethorphan HBr	Novartis
17	Triaminic	Phenylephrine HCl	Novartis
18	Donepezil	Donepezil HCl	Labtech
19	Sudafed	Phenylephrine HCl	Pfizer
20	Rapid film	Ondansetron	GmbH
21	Klonopin wafers	Clonazepam	Solvay pharmaceuticals
22	Listerine cool mint pocket packs	Cool Mint	Cool Mint

23	Listerine	Cool mint	Pfizer
24	Sudafed PE	Phenylephrine	Wolters Kluwer Health Inc.

Conclusion

Fast dissolving films are intended to be applied in the mouth and it is a highly unique dosage, especially for pediatric and geriatric patients. These dosage forms are critical in emergency situations such as allergic reactions and asthmatic attacks, where the immediate onset of action is desired. Sublingual absorption is efficient because the percentage of medicine absorbed is often higher than that attained via the oral route. As a result, oral thin films are a recognized method for systemic API distribution.

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