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Review Article

Fast Dissolving Sublingual Film - A Review

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ABSTRACT

Fast dissolving sublingual films is an emerging technology with rapid onset of action and improved patient compliance. It improves the efficacy of API's and provides better drug utilisation. These formulations are suitable for cold, allergic rhinitis, asthma attacks, CNS disorders etc. where rapid onset of action is required for faster relief. The sublingual route of drug administration is very effective since, the drug absorbed through the sublingual blood vessels by passes hepatic first pass metabolic process and gives a better bioavailability. The present article overviews the materials used, formulation aspects, manufacturing methods, evaluation parameters and applications of fast dissolving films by sublingual route. Many patients find it difficult to swallow tablets and hard gelatin capsules particularly pediatric and geriatric patients and do not take their medicines as prescribed. Difficulty in swallowing or dysphasia is seen to afflict nearly 35% of the general population. In some cases such as motion sickness, sudden episode of allergic attack or coughing and an unavailability of water, the swallowing of tablet or capsules may become difficult, in such situation fast dissolving drug delivery system is alternative mode administering the drug.

INTRODUCTION

Fast dissolving film is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration and recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance [1].

The fast dissolving drug delivery systems was an advancement that came into existence in the early 1970's and combats over the use of the tablets, syrups, capsules which are the other oral drug delivery systems. Fast dissolving drug delivery systems serves as a major benefit over the conventional dosage forms since; the drug gets rapidly disintegrated and dissolves in the saliva without the use of water [2].

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Some patients have difficulty in swallowing or chewing solid dosage forms which risk or fear of chocking and thus is a major problem in the use of solid dosage forms. So, to eliminate this drawback fast dissolving films can be developed. Fast dissolving film (FDF) is a new drug delivery system for oral drug delivery. FDF is used in acute conditions such as pain, emesis, migraine, hypertension, congestive heart failure, asthma etc. These are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, ease of swallowing, rapid onset of action and convenience of dosing [3, 5].

This delivery system consists of a thin film, is simply place below the tongue, instantly wet by saliva and the film rapidly dissolves. Then, it rapidly disintegrates and dissolves to release the medication for systemic absorption. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist sublingual environment [6].

FDFs are useful in patients such as pediatrics, geriatrics, bedridden, emetic patients, diarrhea, and sudden episode of allergic attacks or coughing for those who have an active life style. It is also useful where local action is desired such

as local anesthetic for toothaches, oral ulcers, cold sores or teething [7].

Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained in to systemic circulation. The sublingual route can produce a rapid onset of action within a short period of time due to high permeability and vascularisation of the sublingual mucosa [8].

Overview of the Oral Cavity [9]

The oral mucosa is made out of an outermost layer of stratified squamous epithelium. Beneath this lies a basement membrane, alamina propria followed by the submucosa as the innermost layer. The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is assessed that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. There are extensive differences in permeability between different regions of the oral cavity because of the various structures and functions of the different oral cavity.

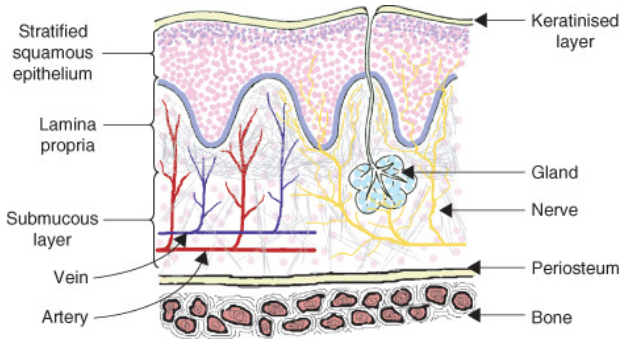

Figure 1: Oral Mucosa

Sublingual Glands [10]

Salivary glands are present in the floor of the mouth underneath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. The absorption is transfer of the drug from its site of administration into systemic circulation, so it can be said that absorption is directly proportional to layer thickness. The absorption of the drug follows in this sequence Sublingual > Buccal > Gingival > Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent.

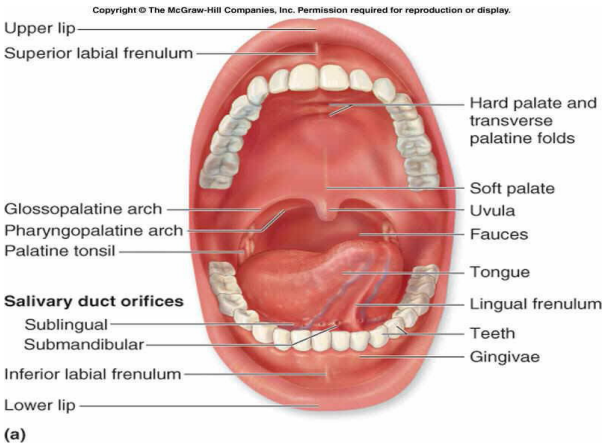

Figure 2: Sublingual gland

Sublingual Absorption

The absorption capability of the buccal mucosa is impacted by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH), and the molecular weight of the substances. For example, absorption of few drugs via the buccal mucosa is shown to increase when carrier pH is lowering (more acidic) and decrease with a lowering of pH (more alkaline) 7.9 [11].

The cells of the oral epithelium and epidermis are additionally fit for retaining by endocytosis (the uptake of particles by a cell as though by hollowly wrapping itself around it. These inundated particles are generally excessively vast to diffuse through its divider). It is impossible that this mechanism is utilized over the whole stratified epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is accepted that acidic stimulation and uptake into the circulatory system [12].

Factors Affecting on Sublingual Absorption of Drug [13]

Lipophilicity of drug: For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.

Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in

aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.

pH and pKa of the saliva: As the mean pH of the saliva is 6.0 and this pH favours the absorption of drugs which remain unionized and also the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acidic drugs and less than 10 for a basic drugs.

Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.

Thickness of oral epithelium: The thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

Criteria for Sublingual Fast Dissolving Drug Delivery System[14]

- Water is not require to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Should be compatible with taste masking.
- Should be portable without fragility concern.
- Should have a pleasant mouth feel.
- It should leave minimum or no residue in the mouth after oral administration
- It should exhibit low sensitive to environmental condition as temperature and humidity.
- It should allow the manufacture to use conventional processing and packaging equipments at low cost.

Advantages of Sublingual Fast Dissolving Films [15, 16]

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- Convenience in administration of drug and accurate dosing as compared to liquid formulations.
- Water is not required for swallowing the dosage form, which is convenient feature for patients who are travelling and do not have immediate access to water.
- Thin film is more stable, durable and quick dissolving than other conventional dosage form.
- Thin film enables to improve dosage accuracy relative to liquid formulations, since every strip is manufactured in such a way that it contains a absolute amount of the drug.
- Permits continuous drug administration and the use of drugs with a short biological Half-life.
- Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds.
- The first pass effect can be avoided, so a reduction in the dose which can prompt to decrease in side effects associated with the molecule.
- It also avoids the risk and inconveniences of intravenous therapy.

Disadvantages of Sublingual Fast Dissolving Films

- Since sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- Although this site is not well suited to sustained delivery systems.
- Sublingual medication cannot be used when a patient is unconscious or uncooperative.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease of the medication.
- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- These films are moisture sensitive and expensive packing of oral film is required.

Formulation of Fast Dissolving Films [17- 20]

Mouth dissolving film is a thin film with an area of 5-20 cm^2 containing an active ingredient. The immediate dissolution of films in water or saliva is reached through a special matrix from water-soluble polymers. A composition for formulation of fast dissolving films was given in Table 1.

Table 1: Composition of fast dissolving films

S. No	Composition	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.	Flavouring agent	10%
7.	Colouring agent	1%

1. Active Pharmaceutical agent (Drugs)

The drugs selected for oral films should possess good stability in saliva and water with low dose. The film should consist of 1-25% w/w of the drug. Small dose molecules are the best candidates to be incorporated in oral fast dissolving films. Multivitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. 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 oral fast dissolving films.

Table 2: Drugs that can be used in fast dissolving films

Active pharmaceutical Category	Therapeutic category	Dose
Nicotine	Smoking cessation	1-15mg
Nitroglycerin derivatives	Vasodilator	0.3-0.6mg
Zolmitryptan	Anti migraine	2.5mg
Sumatripten succinate	Ant migraine	35.0-70.0mg
Tiprolidine hydrochloride	Antihistaminic	2.50mg
Loratidine	Anti histaminic	5-10mg
Omeprazole	Proton pump inhibitor	10-20mg
Ketoprofen	Anti inflammatory	12.5-25mg
Chlorhexidine gluconate	Anti microbial	0.12%
Oxycodone	Opoid analgesic	2.5-10mg
Dicyclomine	Muscle relaxant	25mg

2. Film forming polymer

The polymers can be used alone or in combination to obtain the desired strip properties. Both natural as well as synthetic polymers can be used in the formulation of oral films. To formulate films, excipients or polymers used must be water soluble with low molecular weight and excellent film forming capacity. The polymer used must be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. At least 45% w/w of polymer should generally be present based on the total weight of dry film.

The various natural as well as synthetic polymers to make fast dissolving films include cellulose or cellulose derivatives, Pullulan, Gelatin, Hypromellose, Hydroxyethyl cellulose, Hydroxypropyl cellulose, PVP, Carboxymethyl cellulose, PVA, Sodium alginate, Xanthan gum, Tragacanth gum and Guar gum etc.

3. Plasticizers

It helps to improve the flexibility of the strip and reduces the brittleness of the film. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. Glycerol, low molecular weight Propylene glycols, Phthalate derivatives like Dimethyl, Diethyl and Dibutyl phthalate, Citrate derivatives such as Tributyl, Triethyl, Acetyl citrate, Triacetin and Castor oil are some commonly used plasticizer. The plasticizers are used in the concentration of 0-20% w/w of the dry polymer weight.

4. Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of secretion of saliva that would aid in the faster disintegration of the rapid dissolving films. These agents are used alone or in combination between 2-6% w/w of the films. Citric acid, Malic acid, Lactic acid, Ascorbic acid and Tartaric acid are the few examples of salivary stimulants.

5. Sweetening agents

Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and Isomaltose. Polyhydric alcohols such as Sorbitol, Mannitol and Isomaltose can be used in combination as they additionally provide good mouth feel and cooling sensation. The artificial sweeteners like Saccharin, Cyclamate and Aspartame are the first generation of the artificial sweeteners followed by Sucralose, Alitame and Neotame which fall under the second generation artificial sweeteners. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

6. Flavouring agents

Preferably up to 10%w/w flavours are added in the Fast dissolving film formulations. The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavour quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The geriatric population like mint or orange

flavours while younger generation like flavours like Fruit punch, Raspberry etc. Flavouring agents can be selected from the synthetic flavour oils, Oleo resins, extracts derived from various parts of plants like leaves, fruits and flowers. Any flavour can be added such as essential oils or water soluble extracts of Menthol, Intense mints such as Peppermint, Sweet mint, Spearmint, Wintergreen, Cinnamon, and Clove, Sour fruit flavour such as Lemon, Orange or Sweet confectionary. Flavours such as Vanillin, Chocolate or fruit essence like Apple, Raspberry, Cherry, and Pineapple.

7. Colouring agents

A full range of colours is 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 pantonematched colours.

Manufacturing Methods [21- 24]

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

2. Semi solid casting method

In semisolid casting method the 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 films or ribbons using heat controlled drums, dried, made it into suitable sizes.

3. Hot melt extrusion method

In hot melt extrusion method the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion.

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

4. Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5. Rolling method

In rolling 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 cut in to desired shapes and sizes.

Evaluation Parameters for Sublingual Film [25-29]

1. Thickness

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

2. Weight variation

Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

3. Folding endurance

Folding endurance was determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

4. Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below:

Tensile strength = Load at failure × 100/ Film thickness × film width

5. Percent elongation

A film sample stretches when stress is applied and it is referred to as strain. Strain is basically the deformation of film divided by original

dimension of the sample. Elongation of film increases as the plasticizer content increases.

Percent Elongation= L * 100/ Lo

Where,
L = Increase in length of film,
Lo = Initial length of film.

6. Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5ml of distilled water and kept for 30sec.The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1min. The average of three determinations for each formulation was done.

7. Uniformity of drug content

This parameter was determined by dissolving one film of dimension 2 x 2 cm^2 by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking. From this, 1 ml was withdrawn and diluted with simulated salivary fluid. The absorbance was measured using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations and average values were recorded.

8. *In vitro* dissolution studies

Dissolution profile of fast dissolving films was carried out using USP type II (paddle apparatus) with 300 ml of simulated salivary fluid (pH 6.8) as dissolution medium, is maintained at 37 ± 0.5 ^oC and was stirred at 50 rpm. Samples were withdrawn at every 30 seconds interval and replacing the same amount with the fresh medium. The samples were analysed by UV spectrophotometer. The percentage drug release was calculated and it was plotted against time.

9. *Ex vivo* permeation studies through porcine oral mucosa

Permeation studies were carried using the modified Franz diffusion cell of internal diameter of 2.5 cm. The buccal pouch of the freshly sacrificed pig was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.6 and used immediately. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 200 ml of isotonic phosphate buffer of pH 7.4 which was maintained at 37 ± 0.2ºC and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One film of dimensions 2 x 2 cm^2, previously weighed, was placed in intimate contact with the mucosal surface of the membrane that was previously moistened with a few drops of simulated saliva. The donor compartment was filled with 1 ml of simulated saliva of pH 6.8. Samples were withdrawn at suitable interval, replace the same amount with the fresh medium. The percentage of drug permeated as determined by measuring the absorbance by using UV Visible Spectrophotometer.

10. Stability studies

The stability study of the formulated film was carried out under different experimental conditions. The film was wrapped in butter paper and then packed in aluminum foil and kept at room temperature in stability chamber at 45–50 ^oC and 75% RH for the period of 90 days. After this period, films were characterized for drug content and other evaluation parameters.

PACKAGING [30-32]

In the pharmaceutical industry, it is vital that the package selected adequately should preserve the integrity of the product. Expensive packaging, specific processing and special care are required during manufacturing and storage to protect the dosage of fast dissolving dosage forms. Single packaging is mandatory for films. An aluminum pouch is the most commonly used packaging material for oral fast dissolving films. Variety of packaging options is available for fast dissolving films are as follows:

1. Foil, paper or plastic pouches

The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling or sealing equipment.

2. Single pouch and Aluminum pouch

Soluble film drug delivery pouch is used for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display and using a 2 structure combination allows for one side to be clear and the other to use a cost effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and

pharmaceutical application. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

3. Blister card with multiple units

The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat-softening sheet of thermoplastic resin and vacuum- drawing the softened sheet of plastic into a contoured mould. After cooling the sheet is released from the mould and proceeds to the filling station of the packaging machine. The semi rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

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