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Review Article

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REVIEW ON FAST DISSOLVING SUBLINGUAL FILMS

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ABSTRACT

Fast dissolving drug delivery system dissolves in saliva without the need for water and disintegrates quickly. Fast Dissolving Drug Delivery Systems offer a significant advantage over conventional dosage forms. It produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath the tongue. Fast dissolving sublingual film can be formulated using different approaches like solvent casting method, semisolid casting method, hot melt extrusion method, solid dispersion extrusion method, rolling method. The sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. This review highlights on different approaches for sublingual dosage forms, factor affecting the sublingual absorption, advantages and disadvantages, various evaluation parameters for the sublingual films.

KEYWORDS: Fast dissolving sublingual film, Solvent casting method, hot melt extrusion, rolling method.

INTRODUCTION

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.[1]

Fast dissolving drug delivery system dissolves in saliva without the need for water and disintegrates quickly. Fast Dissolving Drug Delivery Systems offer a significant advantage over conventional dosage forms. Because of its high blood flow and permeability, the oral mucosa allows medications to have a quick onset of action, a long onset time, and immediate absorption.[2]

When a medication is administered sublingually, it is positioned beneath the tongue and enters the bloodstream through the floor of the mouth and the tongue's ventral surface. The medication solutes are quickly absorbed into the reticulated vein, which is located beneath the oral mucosa. From there, they are transferred via the internal jugular vein, braciocephalic vein, and facial veins before being emptied into the systemic circulation. Passive diffusion into the lipoidal membrane is the primary process by which the medication enters the oral mucosa.[3,4]

Fig 1: Sublingual route of administration.

Sublingual gland[5]

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 interior area of the mouth remains lubricated due to production of the saliva by the glands, which is necessary for chewing and food swallowing. The absorption occurs by 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. 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. The drug gets diluted in the saliva

and from there the drug is adsorbed across the oral cavity.

Permeability[6]

The sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area. The differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered.

Mechanism of absorption[7]

The mucosal lining consists of three distinct layers. The outermost layer is the epithelial membrane, which consists of stratified squamous epithelial cells and has a protective barrier function. The innermost layer of the epithelial membrane is called the basement membrane that replenishes the epithelium. Below the epithelium lies the lamina propria followed by the submucosa. The oral submucosa is also richly supplied with blood vessels. Following the absorption through mucous membrane in the sublingual region, drug instantly diffuses into venous blood. The venous blood from sublingual region of the oral cavity drains into a common trunk, which then drains via the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cava. Thus, venous return from these regions enter the systemic circulation, bypassing the pre-systemic drug elimination, unlike in oral administration. Direct drainage into systemic circulation results in the immediate systemic availability of the drug and rapid onset of action.

Formulation consideration[8,9,10,11]

Composition of sublingual films

Sl. No	Composition of films	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

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.

2. Film forming polymers

Polymers play an important role in the formation of film. Hydrophilic polymers are mainly used in the preparation so that film dissolves rapidly in the oral cavity and drug is delivered to the systemic circulation via dissolution when it comes in contact with the saliva in the buccal cavity. Film forming polymers can be used alone or in combination in a film to get the desired film properties. Robustness of film depends on the amount and type of polymer in the formulation. Both synthetic and natural polymers are used in the oral cavity. Natural polymers are effective, safe and avoid side effect so they are more preferred than synthetic polymers. The water-soluble polymers result in good mouth feel, rapid disintegration and mechanical properties to the film.

3. Plasticizer

Plasticizer is an essential component of the quickly dissolving films that helps to increase the strip's flexibility and lessen its brittleness. It lowers the polymer's glass transition temperature, which enhances the film-forming qualities. The choice of plasticizer will be based on how well it works with the polymer and what kind of solvent is used in the film casting process. With plasticizer, the polymer's flow will improve and its strength will be increased. Among the frequently used plasticizers include glycerol, propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate, and citrate derivatives including tributyl, triethyl, acetyl citrate, triacetin, and castor oil. Plasticizers are typically utilized in the concentration of 0–20 percent; w/w of dry polymer weight. Inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. The use of certain plasticizers may also affect the absorption rate of the drug.

4. Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster dissolution of the film formulations. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

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. Flavouring agent

Fast dissolving film compositions should contain up to 10%w/w flavours. An individual's approval of an oral disintegrating or dissolving formulation is mostly determined by the initial flavour 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 prefer mint or orange flavours, whilst the younger generation prefers fruit punch, raspberry, and so on. Flavouring agents can be chosen from synthetic flavour 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.

Advantages of fast dissolving sublingual films[12,13]

- It produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath the tongue.
- Dose gets reduced.
- Onset of action is very fast.
- Improved bioavailability.
- Fewer side effects.
- Effective in disease like nausea, vomiting, migraine, schizophrenia.
- No need of water for administering tablet.
- Ease of drug administration gets increased.
- Sublingual area is much more permeable than buccal area.
- Improved patient compliance.
- pH in the mouth is relatively neutral so drug will be more stable pH in the mouth is relatively neutral so drug will be more stable
- bypass GI tract and hepatic portal system and avoid hepatic first pass metabolism due to this bioavailability of drug get increase.
- Avoid the risk of chocking
- Palatable

Disadvantages[14]

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs with high dose cannot be incorporated into the film
- Drugs which irritate the mucosa cannot be administered by this route
- As it is fragile and must be protected from water, it requires special packaging.

Characteristics of drugs for sublingual administration[15]

- Good stability in water and saliva.
- Partially non-ionised at the oral pH
- Small to moderate molecular weight.
- Dose lower than 20mg.

Factors affecting the sublingual absorption[16]

Thickness of oral epithelium

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

Lipophilicity of drug

For a drug to be absorbed completely through sublingual route, it must have slightly higher lipid solubility than that required for GI absorption.

pH and pKa of the saliva

As the mean pH of the saliva is 6.0, this favours the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.

Oil to water partition coefficient

Compounds with favourable oil - water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient ranges of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Solubility in salivary secretion

In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of the drug is necessary for absorption.

Binding to oral mucosa

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

METHOD OF PREPARATION OF SUBLINGUAL FILMS[17,18,19]

Sublingual films are prepared by five methods.

• Solvent casting method
• Semisolid casting method
• Hot melt extrusion method
• Solid Dispersion Extrusion Method
• Rolling method

Solvent Casting Method

In this method the water-soluble ingredients are dissolved to form a clear and transparent viscous

solution. The drug and other excipients are dissolved in small amount of the solution and mixed with the bulk. The whole mixture is blended thoroughly in a cyclomixer to form a homogeneous solution. The entrapped air bubbles are removed by applying vacuum. The final solution is casted in moulds as films and allowed to dry. The films are stored in a dessicator to prevent the loss of moisture.

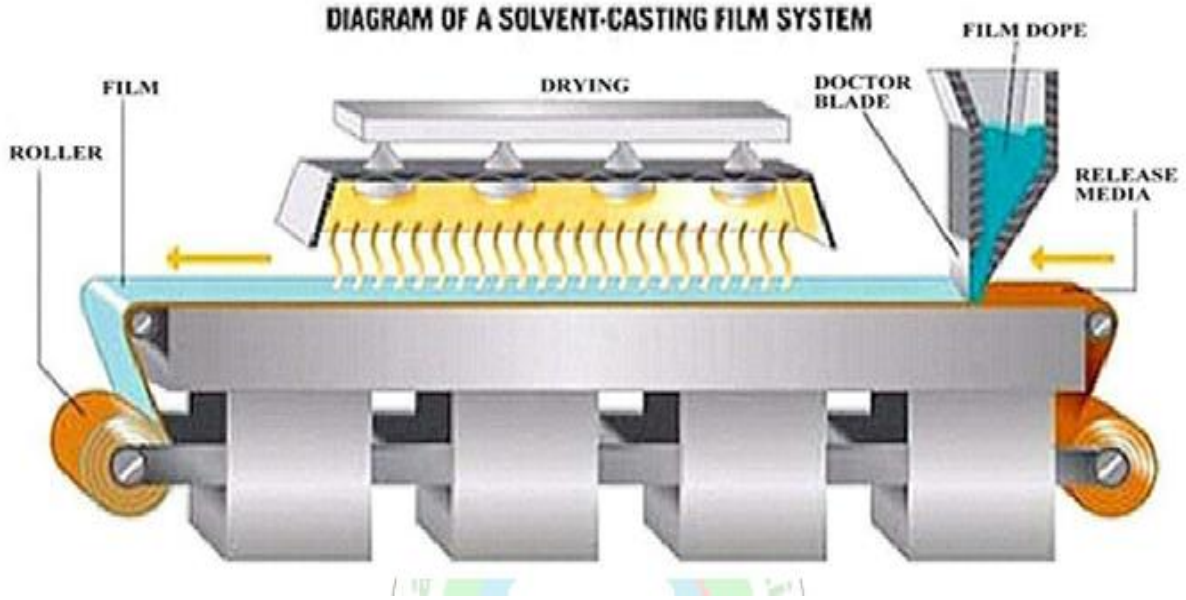

Fig 2: Solvent casting method.

Semisolid Casting Method

This method is mainly adopted when acid insoluble polymers are used in formation of films. In this method the mass of gel is casted into films with the aid of heat-controlled drums. Gel is obtained by adding solution of the film to the solution of acid insoluble polymer in alkali solution like ammonium or sodium hydroxide. Acid insoluble polymers used are generally cellulose derivatives like Cellulose acetate phthalate, Cellulose acetate butyrate. Acid insoluble polymer and film forming polymer are used in the ratio 1:4.

Hot Melt Extrusion Method

In this method drug is mixed with the carrier, granulated and passed through an extruder. The speed of the screw is set at 15 rpm in order to process the granules in extruder within 5 min. The granules are subjected to different temperatures in different zones ranging from 80^{o}C to 115^{o}C. The extrudate maintained at a temperature of 115^{o}C is compressed to obtain films which are later pouched and sealed.

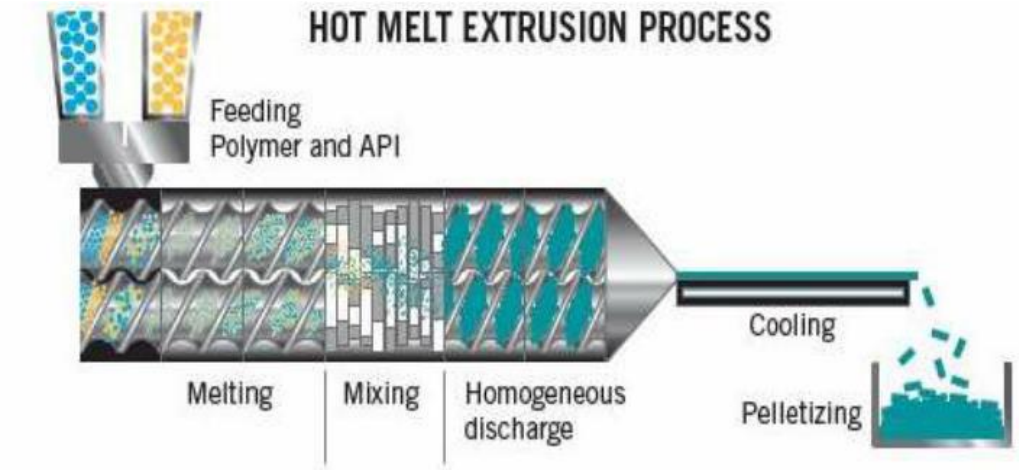

Fig 3: Hot melt extrusion method.

Solid Dispersion Extrusion

In solid dispersion method drug is mixed with immiscible components to form a solid dispersion which is extruded and finally casted as films in the die cavity.

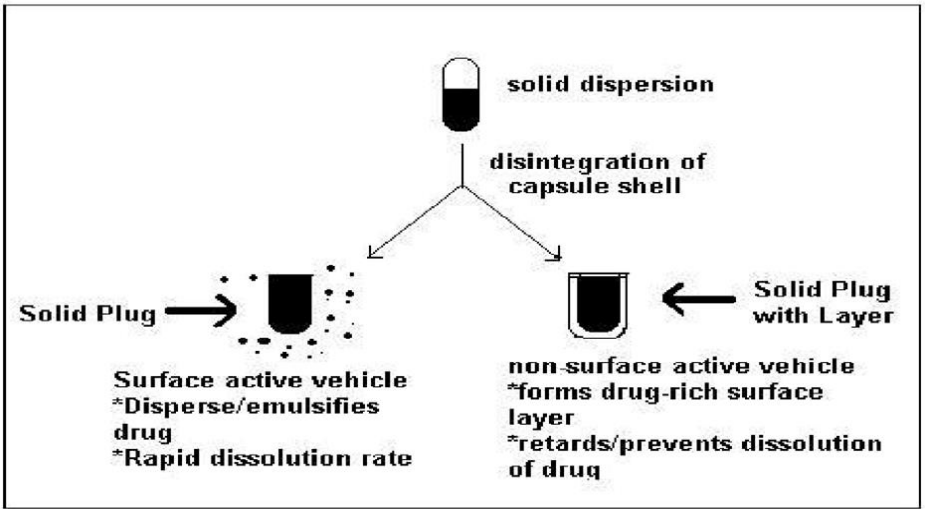

Fig 4: Solid dispersion extrusion.

Rolling Method

In rolling method drug is incorporated in the polymer as a solution or suspension formed either in water or in a mixture of water and alcohol having certain rheological specifications and then dried on rollers and finally cut into desired dimensions.

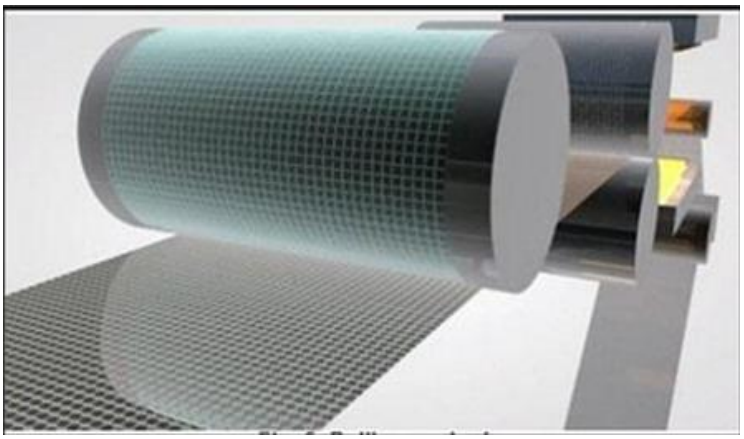

Fig 5: Rolling method.

Evaluation parameters

Visual appearance[20]

Physical appearance of the film is checked by visual inspection and surface texture is evaluated by touch or feel of the film.

Weight variation[21]

Two square inch film is cut at five different places in the cast film. The weight of each film/ strip is taken and the weight variation will be calculated.

pH measurement[22]

The film to be tested is placed in a petridish and moistened with 1ml of distilled water and keep for 30s. The pH will be 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 is done.

Thickness[23]

The thickness of the film is determined using a micrometre screw gauge. Five films from each formulation will be used and average values will be calculated. It is expressed in mm.

Tensile strength[24]

Tensile strength of film is measured using tensile strength apparatus. The sample of film (dimension of 3x3 cm^2) will be held vertically between two clamps. The force at which the film starts to break is noted.

$$\text{Tensile strength} = \frac{\text{load at breakage}}{\text{strip thickness} \times \text{strip width}}$$

Folding endurance[25]

Folding endurance of the films determine the flexibility of the films. It will be determined by repeatedly folding a small strip at the same place until it breaks. The number of times strips could be folded at the same place, without breaking gives the value of folding endurance.

Swelling index[26]

Measuring of swelling index of oral film will be conducted in phosphate buffer of pH 6.8. The oral strip sample (surface area 3x3cm^2) is weighed by using digital

weight machine and placed in a pre-weighed wire sieve. The wire sieve containing sample film will be put into 10ml of phosphate buffer of pH 6.8 in a petridish. At definite time intervals, wire is removed. Increase in weight of the film will be determined at each time interval until a constant weight is observed. The degree of swelling is calculated using the formula,

Swelling index = $\frac{Wt-W1}{W1}$

Where, w_t is weight of the film at time t and
w_1 is weight of the film at time zero

Drug content[27]

The film of specific area (3x3cm^2) will be cut and transferred to a graduated flask containing 100ml of phosphate buffer pH 6.8 and stirred on a magnetic stirrer for 4h. The solution is then filtered and diluted using the phosphate buffer pH 6.8. The absorbance will be measured using UV spectrophotometer.

***In vitro* disintegration study**[28]

The *in vitro* disintegration time of the formulations will be determined by petri dish method. Phosphate buffer (pH 6.8) will be placed in a clean dry petri dish and the film (3x3cm^2) is placed on its surface. The time required for the complete disintegration of the film will be noted. The test is performed on three strips of each formulation batch and mean ± SD is calculated.

***In vitro* release study**[29]

The *in-vitro* dissolution test is carried out in a USP I dissolution apparatus. The films of appropriate size (3×3 cm^2) will be cut and placed in the basket. The dissolution medium consists of 300 ml freshly prepared phosphate buffer (pH 6.8), maintained at 37 ± 0.5 ºC and stirred at 50 rpm. Samples of 5 ml will be withdrawn at predetermined time intervals & replaced with fresh medium. The samples will be subjected to UV analysis.

Stability study[30]

Films are stored at two different storage conditions i.e. 30°C/60% RH and 40 °C/75% RH. Each film will be wrapped in a butter paper followed by aluminum foil and placed in an aluminum pouch, which will be sealed at the end. The films will be evaluated for appearance, weight, Drug content and *in vitro* drug release after storage for 30, 60 and 90 days.

CONCLUSION

It is concluded from the review that fast dissolving sublingual film can be a promising formulation for improving bioavailability of large number of drug. This formulation overcome the drawback of oral solid dosage form. In this formulation drug rapidly release into the systemic circulation and shows immediate action.

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