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A REVIEW ARTICLE ON FAST DISSOLVING SUBLINGUAL FILM

Vaishali D. Sangale*[1], Smita S.Aher[2], Ravindra B.Saudagar[2]

[1]Department of Quality Assurance Techniques, R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.

[2]Department of Pharmaceutical chemistry, R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.

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Fast dissolving drug delivery, oral strips, sublingual film, Mouth dissolve

For Correspondence:

Vaishali D. Sangale

Department of Quality Assurance Techniques, R.G.Sapkal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India.

E-mail:

vaishalisangale90@gmail.com

ABSTRACT

Orally fast dissolving films are an emerging technology with fast onset of activity and improved patient compliance. It enhances the viability of API's and gives better medication use. These formulations are suitable for cold, allergy rhinitis, asthma attacks, CNS issue where fast onset of activity is needed for quicker help. The sublingual course of medication organization is extremely compelling following the medication retained through the sublingual veins by passes hepatic first pass metabolic procedure and also gives a better bioavailability. The present article outlines the definition viewpoints, manufacturing methods like solvent casting method, evaluation parameters and applications of fast dissolving films by sublingual routeIt has been estimated that approximately 84% of all sales of the top selling commercially available products are delivered via the oral route. Thin film drug delivery has come forward as an advanced alternative to the traditional tablets, capsules and liquids frequently associated with prescription and OTC medications. Similar in size, shape, and thickness to a postage stamp, thin film strips are classically designed for oral administration, with the user placing the strip on or under the tongue(sublingual)or along the inside of the cheeks(buccal).These drug delivery options allows the medication to bypass the first pass metabolism thereby making the medication further available. As the strip dissolves, the drug can enter the blood stream enterically, buccally or sublingually. The permeation is superior with sublingual than buccal than palatal region.

INTRODUCTION

The Fast Dissolving Drug Delivery Systems was a headway that started to be in the early 1970's and combats over the utilization of the tablets, syrups, capsules which are the other oral drug delivery system. Fast Dissolving Drug Delivery Systems serves as a real benefit over the conventional dosage forms since the drugs gets quickly disintegrated & dissolves in the salivation without the utilization of water. The most well known oral solid dosage forms are tablets and containers. Numerous patients find it hard to swallow tablets and hard gelatin capsules especially pediatric and geriatric patients and do not take their medicines as prescribed. Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres on to the site of application. It then rapidly disintegrates and dissolves to release. Trouble in swallowing or dysphagia is seen to afflict almost 35% of the overall population. At times, for example, motion sickness, sudden episode of unfavorably susceptible assault or hacking, dread of gagging and an inaccessibility of water, the gulping of tablet alternately containers may get to be trouble some. To overcome these troubles, a few fast dissolving medication drug delivery system have been created [1,2]

OVERVIEW OF THE ORAL CAVITY[7]

The oral mucosa is made out of a outermost layer of stratified squamous epithelium. Beneath this lies a basement membrane, alaminapropria 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.

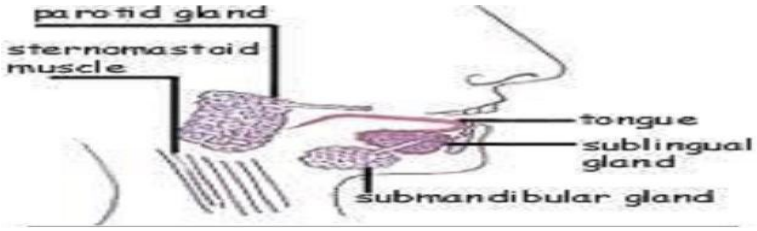

Fig 1- Fig Of Salivary Glands

Sublingual absorption

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.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)

Sublingual gland[8]

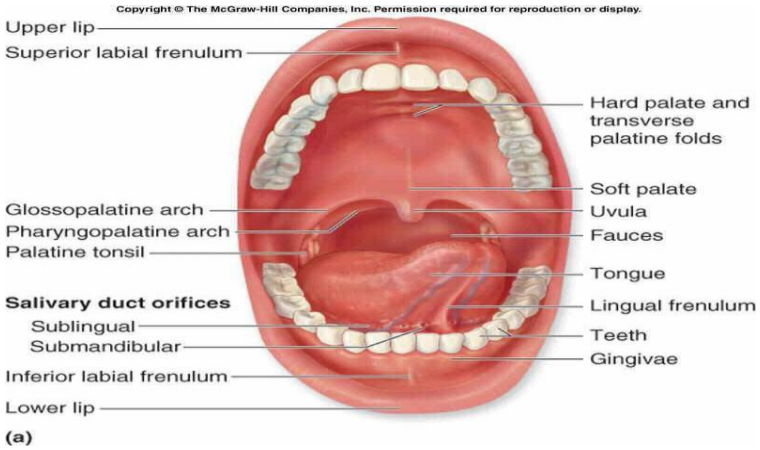

Fig. 2:Figureofsublingual gland

salivary glands are available in the floor of the mouth underneath the tongue. They are also known as sublingual glands. They produce mucin in turn produces saliva. The inner area of the mouth stays lubricated due to production of the saliva by the glands, which is necessary for, chewing and food swallowing. The fluid which is produced by the glands gets blend with the food, so the food gets easily chewed. Due to low secretion of the saliva it can create problem in swallowing the food and potential for food lodge in the throat increases. 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 layer thickness. The absorption of the drug is like Sublingual

> Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can deliver fast onset of action so the drug with short delivery period can be delivered and dose regimen is regulars. The drug gets diluted in the saliva and from there the drug is adsorbed across the oral cavity.

FACTORS AFFECTING THE SUBLINGUAL ABSORPTION [14]

Lipophilicity of Drug

For a drug to be absorbed absolutely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is all-important 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 all-important for absorption.

pH and pKa of The Saliva

As the mean pH of the saliva is 6.0, this pH favors 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.

Binding to Oral Mucosa

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

Th**ickness of Oral Epithelium**

As 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 as well the immersion of drug in smaller volume of saliva.

ADVANTAGES [30]

1. Accessibility: The oral cavity offers a very accessible surface for drug delivery, both for the application and removal of drug delivery systems. This accessibility omits the need for complex delivery devices to enable the drug to reach its absorption site. Thus devices for an oral delivery are simpler in design than those intended to deliver drugs to, the alveolar region of the lung.

2. **Relatively large surface area:** The oral cavity offers a relatively large surface area (the total area of the buccal cavity is approximately 100 cm^2) for, both from the application and relatively drug absorption.

3. **Rich blood supply**: The highly vascular surface of the oral mucosa ensures rapid absorption and onset of action, as well as the maintenance of sink conditions. In particular, the sublingual route is characterized by rapid onset of action. The buccal offers the combined advantages of relatively rapid onset of action, with the potential for sustained delivery over several hours.

4. Ease of use: Oral Trans mucosal devices, such as sprays, tablets or patches, are also simple for the patient to use and might be expected to be more acceptable to the patient than use of pessaries or suppositories for the intravaginal and rectal delivery routes respectively.

5. **Low variability**: This route has less variability than, for example, the oral route, where factors such as intestinal motility, presence of food and extremes of pH combine to make oral drug delivery highly variable. However, factors such as salivary flow and certain diseases states can contribute to a degree of variability associated with this route.

6. **Low metabolic activity:** The metabolic activity of the oral cavity is thought to be less than that of the GI tract, which making this route an attractive alternative to the oral delivery of the enzymatically labile drugs such as therapeutic peptides and proteins. Furthermore, this route avoids first-pass effects of degradation in the intestinal wall or the liver (Hepatic metabolism), prior to the drug reaching the systemic circulation.

7. **Robust**: The oral mucosa is routinely exposed to a multitude of different foreign compounds and is relatively robust and less prone to irritation than, for example, the nasal mucosa.

8. **Zero-order controlled release:** Buccal drug delivery offers the potentive to achieve zero-order controlled release. Zero-order controlled release offers advantages of:

-avoiding the peaks that is (risk of toxicity) and troughs (risk of ineffectiveness) of conventional therapy;

-reducing the dosing frequency;

-increasing patients compliance.

9. Prolonged retention: Prolonged retention of the drug is possible in the buccal cavity, if the appropriate delivery is used. This allows a lowering of the dosing frequency.

10. **Intestinal alternatives**: The buccal cavity is a useful alternatives to the intestinal route for drug absorption in situations where the gastrointestinal route is unfeasible.

Example include: -patients with nausea and vomiting; -patients with swallowing difficulties;

-for drugs that cause gastric irritation; -for drugs that are unstable in the gastrointestinal fluid

-for drugs that undergo extensive first-pass effects in the gut wall or liver

DISADVANTAGES[29,11 ,30]

1. Limited to potent molecules: For drugs of a high molecular weight (weight thus are poorly absorbed), the route is limited only to potent drug molecules, typically those with effective plasma concentrations within or below the ng mL^{-1} range.

2. Adverse reaction: Locally irritating or sensitizing drugs must be used with caution in this route. However as per overview, the oral epithelium is relatively robust and this factor is not a limiting as in other highly sensitive mucosal sites, such as nasal cavity.

3. Metabolic activity: While the metabolic activity of the oral cavity towards peptides and proteins is less than that of the GI tract, it should be recognized that the oral mucosa secretions do have the ability to degrade drugs and that measures might be necessary to overcome this.

CHARACTERISTICS OF FAST DISSOLVING DELIVERY SYSTEMS (FDDS)[28,26,30]

1. Ease of administration: Fast Dissolving Delivery Systems are easy to administer and convenient for handle hence, these leads to better patient compliance.

In case of, elderly people experience difficulty in swallowing the conventional dosage forms like (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. (FDDS) may offer a solution for these problems.

2. Taste of the medicament: Mouth dissolving delivery systems usually contain the medicament in taste masked form. Taste-masking is found to be having critical importance in the formulation acceptance of FDDS.

3. Hygroscopicity: Several fast dissolving dosage forms mostly are hygroscopic and cannot maintain physical integrity under normal condition from humidity due to sensitive to moisture .so, which should be called for specialized product packaging.

4 Friability: In order to allow fast dissolving films/tablets to dissolve in the mouth, they should made up of both very porous and soft moulded matrices.

5 Mouth feel: Mouth feel is also critical factor, patients should receive a product that feels pleasant. In some instances, any large particles from the disintegrating film/tablet that are insoluble or slowly soluble in saliva may lead to an unpleasant gritty feeling. To overcome this majority of the particles should be kept below the detectable size limit. In some cases, certain flavour can imparts an improved mouth feel perception, which resulting in a product that is perceived as being lessgritty, even if the only change is the flavour. While, Effervescence can be added to aid disintegration and improve mouth feel by reducing the dryness of a product.

Film forming polymers

- A variety of polymers are available for preparation of MDF. Whereas the polymers can be used alone or in combination to obtain the desired film properties.
- Modified starches are also used for preparation of films. Due to low cost of this excipient it is used in combination of pullulan to decrease the overall cost of the product. About 50 to 80%w/w of pullulan can be replaced by starch in the production of oral film without loss of required properties of Pullulan. Typically 60 to 65%w/w of water soluble polymer is preferred for preparation of film with desired properties. Many times, mixtures of polymers are used to improve hydrophilicity, flexibility, mouth-feel and solubility characteristics of film. Polyvinyl pyrrolidone films are brittle in nature and therefore
- Copovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating films.
- Microcrystalline cellulose (MCC) was used to decrease the disintegration time and improve the dissolution of drug from the film.

3. **Plasticizers**

Formulation considerations (plasticizers etc.), have been reported as an important vital factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, phthalate derivatives like di-ethyl, di-methyl, di-butylpthalate, propylene glycol and low molecular weight polyethylene glycols, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and castor oil etc.

4. **Surfactants**

Surfactants are used as solubilizing or wetting or dispersing agent, so that the film is getting dissolved within seconds and release active agents immediately. Some of the commonly used are benzalkonium chloride sodium lauryl sulphate (SLS), benzthonium chloride, tweens etc.

One of the important surfactant is polaxomer 407 that is used as solubilizing agent that is used as solubilizing, wetting, and dispersing agent.

5. **Flavours**

Any flavor can be added, such as intense mints, sour fruit flavours or sweet confectionery flavours. The important aspect of thin film drug technology is its taste and colour. Natural

sweeteners as well as artificial sweeteners are used to improve the flavours of the mouth dissolving formulations for the flavours changes from individual to individual.

6. **Colour**

A full range of colures is available, including FD&C colours, EU Colours, ASTM colours, Custom Pantone matched colours and Natural colours. Some of the saliva stimulating agents may also be added to enhance the disintegration and get rapid release. Some of these agents are tartaric acid, malic acid, ascorbic acid, and succinic acid and mostly used citric acid.[17]

GENERAL METHODS USED FOR PREPRATION MOUTH DISSOLVING FILM [10,9,11,14]

1. Solid dispersion extrusion
2. Semisolid casting
3. Rolling
5. Solvent casting
4. Hot melt extrusion

1. Solid Dispersion Extrusion [25]

In solid dispersion extrusion method all immiscible components is extrude with drugs and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies.

2. Semisolid Casting Method

In this method, at first homogenous solution of water soluble film forming polymer is prepared. Then this prepared solution is added to a solution of acid insoluble polymer. Then approximate amount of plasticizer is added so that a gel mass is obtain. At last the gel mass is casted into the films or ribbon by using heat controlled drums. The thickness of film is about 0.015- 0.05 inches. Whereas, the ratio of the acid insoluble polymers to film forming polymer should be kept 1:4.

Advantages

- Immiscible components can be incorporated in the formulation.
- Bioavailability of drugs is enhanced by solid dispersion method.

3. Rolling Method [23]

In this method, suspension or solution containing drug is rolled on a carrier. The solvent is mainly water or mixture of water and alcohol. The solution or suspension should have a specific rheological consideration. Film is dried on the rollers and cut into desired shapes and sizes .Other

ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

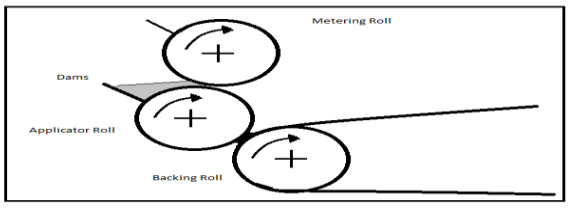

Fig:- Rolling Mill

Advantages

- Thermaldegradationofthedrugdoesnotoccur.
- Adiverserangeofsolventscanbeemployed.

Disadvantages

- Hydrophobicdrugscannotbeemployedintheformulation.
- Flowparametersformacrucialparameterintheprepa-rationoffilmsbythismethod.

3. Solvent Casting Method.[20,21]

In this method, water soluble polymer is completely dissolved in water to form uniform clear viscous solution; all other ingredients including API are dissolved in a small portion of suitable solvent by using a high shear processor. This viscous solution is degassed under the vacuum to remove the air bubbles. This bubble free solution is poured into a suitable glass mold and kept in oven at 40 º-50 º C.

Advantages

- Better thickness,uniformity and appearance ascomparedtoextrusionmethod.
- Filmsformedaretransparentandfreefromdiecavityimperfections.
- Filmshavebetterflexibilityandmechanicalproperties.

Disadvantages

- Boththedrugandpolymerhavetobesolubleinacommonunlikesoliddispersionextrusionmethodwhereincompatiblepolymeranddrugcanbeused.
- Acastedfilmmustnot betackytoavoidtheprobleminremovingfromthemoulds
- Viscosityofthesolutionshould beoptimumsothatthefilmscanbeeasilyhandled.

4. Hot melt extrusion (HME) [22]

Now a day, this method is commonly used to prepare granules and sustained release tablets; also transdermal and trans mucosal drug delivery system. By this technique, preparation of film involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting technique. Hot melt extrusion process based on polymer with a high glass transition temperature such as PVP.

Advantages

- Uniformdispersionduetointensemixing.
- Decreasedlossesofmaterialssincelessunitoperationsareinvolved.
- Mostsuitableforhydrophobicdrugs.
- Hygroscopicmaterialscanbeincorporatedastheprocesstakeplacewithouttheaidofwater.
- Improvethepharmacokineticparametersofhydrophobiccompounds
- Capableofproducingsustains,modified ortargeted thinstripfilms.
- HigherstabilityatevenvaryingtemperatureandpH.

Disadvantages

- Thermostabledrugshavetobeusedsincethecomponentsgetdegradedathighertemperatures.
- Allthecomponentsmustbefreefrommoisturecontent.
- Thepolymersandotherexcipientsshouldhavegoodflowproperty.
- Componentsusedintheformulationshouldhavehighmeltingpointsincethecomponentsshouldnotdegradeathighertemperature.
- Highpowerinputisneeded.
- Binderwithlowermeltingpointcansoftenduringtheextrusionprocessandagglomerate.
- Binderswith higher meltingpointrequire hightemperaturebringingaboutvolatilityproblemforthemolabilematerial.

Equipment used:

- The equipment used for hot melt extrusion consists of extruded, downstream auxiliary equipment and monitoring tools.
- Extruder comprises of a feeding hopper, the barrel, screw, die, screw-driving unit and heating/cooling device.

- Producing thin films for transdermal/transmucosal drug delivery and wound care is via film casting from aqueous or organic solvents. Repka et al studied the influence of Chlorpheniramine maleate on topical HPC films by hot melt extrusion technique.

  Chlorpheniramine has been reported to function as an effective plasticizer, which is increasing percent elongation and decreasing tensile strength in concentration dependent manner. Whereas Chlorpheniramine also acted as a processing aid in the extrusion of hot melt films and allowing film processing at lower temperature.

EVALUATION PARAMETERS FOR FAST DISSOLVING SUBLINGUAL FILM: [25,31]

Several evaluation parameters used for a FDSF is as follows;

1. **Mechanical properties**

Mechanical properties of the films are evaluated using Instron TA.XT2 texture analyzer equipment equipped with a 5 kg load cell. Films are held between two clamps positioned between 3 cm. During measurement the strips were pulled at the rate of 2mm/sec. The force and elongation are measured when film breaks. Three mechanical properties namely tensile strength, elastic modulus and % elongation are calculated.[25]

a) Tensile strength: Tensile strength is calculated by Formula;

Tensile strength= force at break / initial cross sectional area of film in mm^2

b) % Elongation: It is calculated as;

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \text{ X } 100$$

c) Folding endurance:is determined by folding the films of uniform cross sectional area and thickness until breaks.

2. **Morphology study**

The morphology of the films is studied using scanning electron microscopy (SEM), at a definite magnification.

3. **Swelling property**

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighted and placed in a pre weighted stainless steel wire mesh .The mesh containing film sample is submerged into 15 ml medium plastic container. Increase in the film weight is determined at pre-set time interval until a constant weight is observed.

The degree of swelling is calculated using parameters Wt- Wo / Wo, Wt is weight of film at time t, and Wo is weight of film at time zero.

4. **Contact angle**

A contact angle measurement is performed at room temperature with a goniometer (AB Lorentzen and Wettre, Germany).A drop of double distilled water is placed on the surface of the dry film. Images of the water droplet were recorded within 10 seconds of deposition by means by means of digital camera .Digital pictures are analysed by image J1.28v Software (NIH, USA) for angle determination. A minimum of five measurements, taken at different positions of the film, is carried out. The contact angle was measured on both sides of the drop and averaged.

5. **In vitro disintegration time**

In vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate.

6. **In vitro dissolution studies**

The in vitro dissolution study is carried out in simulated saliva solution pH 6.8 phosphate buffer using USP paddle apparatus at 37±0.5^{o}C.Samples were withdrawn at regular time interval and analysed by UV-Visible spectrophotometer. [19]

7. **Surface pH**

The film formulation have to be kept in the oral cavity, pH of saliva ranging from 5.5-7.5.so,to dissolve and solubilise drug in the saliva present in the oral cavity the pH of film should kept near to neutral. If it is acidic one leads to irritation of the buccal mucosa.

CONCLUSION

The oral dissolving films are getting importance in pharmaceutical field. As it offer many advantage over other dosage forms as well as they offer easy production and evaluation technique. This review is an effort to merge the knowledge available on oral dissolving films. A lot of research work is going on and will be started in near future on oral dissolving film.

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