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A Review on Fast Dissolving Sublingual Films as a Promising Drug Delivery Route

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ABSTRACT

Various routes of delivery are available for the delivery of drugs into the body such as oral, transdermal, buccal, sublingual, rectal, parenteral, etc. Out of these the sublingual route of delivery is a good approach for the delivery of drugs via the sublingual route into the systemic circulation. Sublingual films provide a unique opportunity for serving as drug carriers and have the potential for releasing the drug quickly into the sublingual region for rapid absorption and quick effect. Various factors such as the secretion of the salivary glands along with other physiological factors and physiochemical factors of the drug for example hydrophobicity of the drug, binding of the drug to the oral mucosa, the thickness of the epithelium, etc. These parameters need to be taken into consideration for the formulation of an efficient sublingual film drug delivery system. Various evaluation parameters are available for sublingual films namely thickness, weight variation, tensile strength, etc.

INTRODUCTION:

Fast dissolving film is recognized as a newer viewpoint to enhance patient compliance since they provide faster dissolution, can be taken by the patient on his own, and hence have a pivotal role in the pharmaceutical industry because of their special properties coupled with distinct benefits like the absence of water for disintegration, precise dosage regimen, faster therapeutic effect, easy handling, and transportation as well as pleasing taste. [(1)]These rapid dissolving drug delivery systems were an improvement that was born in the early 1970s and battle other oral drug delivery systems for its advantages over them. Such other oral drug delivery systems include tablets, syrups, and capsules. Rapidly dissolving drug delivery systems provide a platform by which drugs have the potential of disintegrating quickly in the saliva that too without the presence of water. Sometimes patients find it hard to swallow or chew solid dosage forms which come with chances of choking or the horror of it and hence presents a big hurdle in the adoption of such solid dosage forms. So there is a need to remedy this situation which fast dissolving films (FDF) are capable of overcoming. FDF is employed in the treatment of short term medical conditions such as pain, emissions, etc as these be their property of dissolving in seconds within the saliva are very much ideal candidates for the above-mentioned conditions.[(2)] Sublingual films are not hard to administer and give a nonstop pathway into the bloodstream bypassing the first-pass metabolism. Sublingual films are very slim and are needed to be kept below the tongue so that they can be speedily dampened by the saliva which further breakdown to liberate the drug and reaches the bloodstream unhindered via the ventral surface of the tongue. Sometimes patients find it hard to swallow or chew solid dosage forms which come with chances of choking or the horror of it and hence presents a big hurdle in the adoption of such solid dosage forms.So there is need to remedy this situation which fast dissolving films (FDF)are capable of overcoming.FDF are employed in the treatment of short term medical conditions such as pain, emissions etc as these be their property of dissolving in seconds within the saliva are very much ideal candidates for the above mentioned conditions.[(3)]

[(4)]The drug is then further captured by the reticulated vein which is present below the oral mucosa and the drug then passes through the internal jugular vein, facial veins, and brachiocephalic vein after which it ultimately gets mixed with the bloodstream.[(5)]

Sublingual Glands:

Salivary glands exist on the floor of the mouth below the tongue. They are also known as sublingual glands which manufacture mucin and then make saliva. This saliva so formed gets amalgamated with the food which makes chewing as well as swallowing less of a trouble. Drug absorption is defined as the movement of a drug from its site of delivery into the bloodstream and this transfer of drug is directly related to how much thick the layer is at that point of absorption. [6]

The absorption of the drug increases in the following order Palatal<Gingival<Buccal<Sublingual. Owing to the greater penetrability and abundant blood supply this route of delivery produces quick action along with less dosage regimen within a lesser time. [7]

Sublingual absorption:

The absorption power of the buccal mucosa is affected by the lipid solubility in addition to osmosis, pH, and molecular weight of the compound. It has been observed that some drugs showed increased permeability when they were formulated in acidic pH and the reverse occurred when basic media was used. The cells present in the oral epithelial as well as epidermis are capable of endocytosis. Such mechanism is not used throughout the mucosa and active transport is also absent in oral mucosa however it is recognized that acidic stimulation is responsible for uptake into the bloodstream. [8,9]

Overview of the oral cavity:

The oral mucosa is built out of an outermost layer of stratified squamous epithelial. The basement membrane is present underneath known as lamina propria after which followed by the submucosa which is the last layer. The oral mucosa is the middle between that of the epidermis and intestinal mucosa when permeability is concerned and is approximately 4 to 4000 times more than the skin. There are vast differences in permeability between different regions within the oral cavity due to the different structures and roles of various regions present within it. [10]

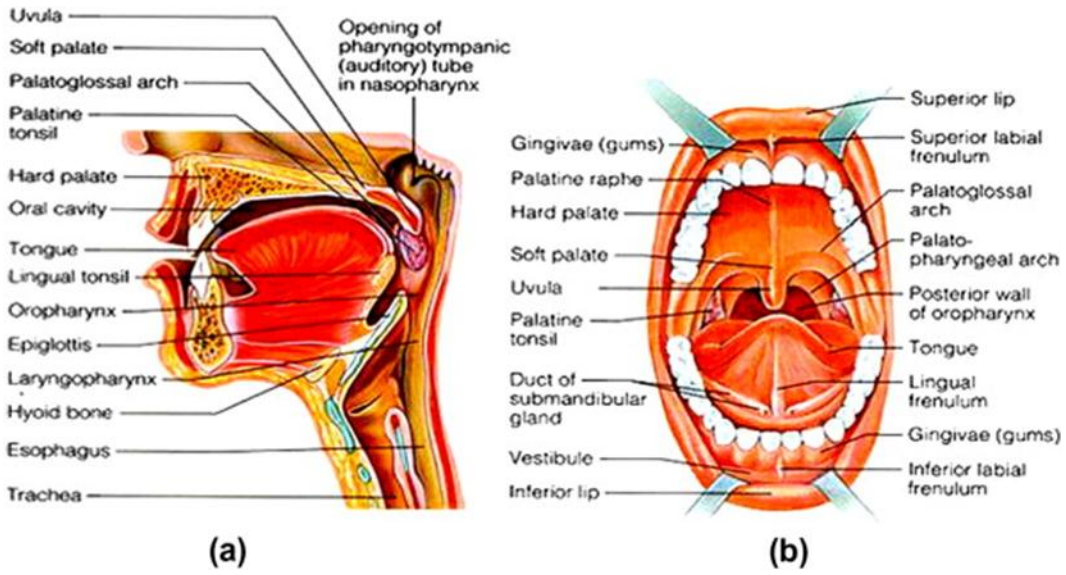

Figure No. 1: Cross-sectional view of the oral cavity

Adapted from Chaudhary H, Gauri S, Rathee P, Kumar V. Development and optimization of fast dissolving oro-dispersible films of granisetron HCl using Box–Behnken statistical design. Bulletin of Faculty of Pharmacy, Cairo University. 2013 Dec 1; 51:193-201.

Factors Affecting on Sublingual Absorption of Drug :[11]

Hydrophobicity of the drug: The condition for the drug to be absorbed perfectly via the sublingual route is that the drug must possess slightly better solubility in lipids than which is needed for GI absorption and subsequent passive diffusion.

Solubility in salivary secretion: The drug should possess dual solubility i.e. it should be soluble in both lipids as well as aqueous buffers as such property is required for the absorption of the drug.

pH and pKa of the saliva: The average pH of saliva is about 6.0 and this pH is suitable for the drug absorption which does not ionize in addition to that drug absorption happens only if the pKa is more than 2 for acidic drugs and it is less than 10 for basic drugs.

The thickness of oral epithelium: The depth of the sublingual epithelial is about 100 to 200 um which is not more when compared against buccal thickness. Hence drug gets absorbed

rapidly as compared to the buccal as the sublingual epithelial is thinner and the drug is also wetted by less volume of saliva.

Criteria for Sublingual Fast Dissolving Drug Delivery System :[12]

1. Water is not needed to swallow but instead, the drug should break down or dissolve in the oral cavity within seconds.

2. It should allow taste-masking ingredients to be incorporated without any reactivity towards those ingredients.

3. It should be easy to carry around and not problematic.

4. It should not leave any remnant in the oral cavity.

5. It should be economical and cheap to manufacture.

6. It should be stable against humidity as well as environmental condition such as temperature and humidity.

Advantages of Sublingual Fast Dissolving Films:[13]

1. This route of delivery is much simpler to administer rather than tablets, capsules in which patients such as geriatric, pediatric as well as psychiatric show resistance to swallow.

2. This route of administration provides comfort to deliver drugs and more precise dosing is possible than liquid dosage forms.

3. Absence of water to use this dosage form is an advantage for people who are traveling and for whom water is difficult to access.

4. The film due to this thinness is much easier to dissolve than other solid dosage forms.

5. First-pass metabolism effects are minimized to a great extent via this route of delivery.

6. It prevents the chances and hazards that associate with parental and intravenous delivery.

7. Provides a platform via which continuous administration of the drug can be given which posses a short half-life.

8. Larger surface area allows quick and rapid disintegration of the film within seconds in the mouth.

Disadvantages of Sublingual Fast Dissolving Films:[14]

1. As sublingual drug delivery poses a problem with eating, drinking as well as taking this route of administration is unsuitable for long term delivery.

2. This site of administration is also not proper for delivering Sustained Delivery systems.

3. Sublingual route of delivery is impossible to the administration of the patient is not conscious or not cooperating.

4. While administering drugs via this route the patient must be restricted from smoking as it causes constriction of the blood vessels and hence reduce absorption capacity.

5. Large doses of drugs are not possible to give.

6. The films possess sensitivity to moisture and packaging is not economical.

7. It is difficult to attain dose uniformity.

Evaluation Parameters for Sublingual Film:[15-19]

Thickness: The thickness of the patch was determined by utilizing digital vernier calipers possessing the least count of 0.01mm at separate points of the film. The thickness was determined at 3 separate points on the patch followed by which mean was taken and SD was calculated.

Weight variation: A square measuring area of 4×4cm was cut from three separate points of the film followed by which weights of all the cut portions were taken and weight variation was determined.

Folding Endurance: This was found out by folding the film at the same place again and again until the film broke apart. The maximum turns by which the film folded without breaking was taken as the folding endurance.

Tensile strength: Tensile strength is the uppermost pressure that is applicable at a place after which the film breaks apart. It is calculated by the pressure applied at that breakpoint divided by the cross-sectional area of the film as mentioned below: same formula: Tensile strength = Load at failure × 100/ Film thickness × film width.

Uniformity of drug content: This parameter is measured by solubilizing a single film having the following dimensions of 2 x2 cm2 by putting it in a homogenized for some time of 30 mins immersed in a 100ml beaker comprising of stimulated saliva of pH 6.8 which is agitated continuously. From this solution take out 1ml of sample and dilute appropriately with simulated salivary fluid and measure absorbance in UV spectrometer. The experiment was carried out thrice and mean values were determined.

Surface pH: The film to be assessed was kept in a petri dish was wetted with 0.5 ml of DW and placed for 30 secs. The pH was determined by allowing the electrode of the pH meter to come.in contact with the formulation and permitting equilibrium for 1 min. This was done in triplicate and the average was calculated.

Percent elongation: A film when put under pressure expands and such phenomenon is known as strain. It is usually deviation from the normal shape which elevates as the force applied elevates.

***In vitro* dissolution studies**: Dissolution studies were performed by utilizing USP type II(Paddle Apparatus) comprising of 300 ml of simulated salivary fluid of pH 6.8 as dissolution medium which is held at 37 ± 0.5°C and RPM was set at 50. At a period of 30 seconds, samples were pipetted out and the amount withdrawn was replaced with a new medium to maintain sink condition followed by which the samples were assessed using a UV spectrophotometer and the percentage release was determined and further plotted against time.

***Ex vivo* studies**: The permeating investigation was done in Franz diffusion cell possessing an internal diameter of 2.5cm. The buccal pouch of the sacrificed pig was bought from a local slaughterhouse. The buccal mucosa was cut and cut in the same dimensions from all sides and then wetted with isotonic phosphate buffer 6.6 and utilized immediately. The mucosa was slapped between the receptor and donor compartments. The receptor compartment was loaded with 200 ml of the buffer of 7.4 pH and which was held at 37±0.2°C and RPM was kept at 30. A film of a specific dimension was weighed and kept with intimate contact with the excised mucosa which was wetted with a simulated salivary fluid of pH 6.8 after which at precise time intervals samples were taken out and analyzed using a UV spectrophotometer.

Stability: Stability studies were done under various experimental conditions. The film was covered in butter paper and then packaged in aluminum foil after which it was kept at room

temperature in a stability chamber at 45-50°C RH for about 3 months. After this time was passed films were again assessed for their evaluation parameters.

PACKAGING:[20,21,22]

In the Pharmaceutical Industry, it is necessary that the packaging material finalized should protect and maintain the quality of the product. As far as fast-dissolving dosage forms are concerned specific and costly materials are needed during processing and also attention needs to be given to storage to preserve the fast-dissolving dosage form.

One Single packaging is compulsory for sublingual films which are further packaged in one of the below materials.

1. **Foil, paper, or plastic pouches**: This elastic pouch is a packaging method that has the capability of giving higher resistance towards environmental damage as well as being damage resistant. Such pouches are made during the product manufacturing process either by vertical or horizontal forming, sealing, or filling equipment.

2. **Single and aluminum pouch**: Special pouches are used for rapid dissolving soluble films providing great barrier properties. This pouch is transparent hence allowing for visual inspection of product from one side in addition to providing economic foil lamination. The foil lamination has the absence of permeating to gas and moisture and hence serves as a promising for nutraceutical applications. Aluminum pouches are the most commonly utilized pouches.

3. **Blister card with multiple units**:

A blister container contains two components first being the blister which has a depression in itself and hence holds the formulation and the second being the lid which seals shut the blister. This blister packaging is manufactured by utilizing a heat softening-sheet of the thermoplastic resin and applying vacuum on the softened sheet of the plastic into a predetermined size mold. After cooling is completed the sheet is liberated from the mold it then goes forward towards the filling line where the formulation is filled within this sheet and is sealed with heat sealable material whereby the material is chosen according to the level of protection required for the formulation. The material used for making the depression within the blister is made up of plastic to act as a barrier from moisture while aluminum is adopted for making the foil.

CONCLUSION

As discussed sublingual films are gaining a lot of attention due to the unique features they provide for drug delivery such as faster delivery of the drug into the systemic circulation, ease of handling, rapid onset of action, etc. Subsequently, the anatomy of the oral cavity along with the functions of each part was discussed followed by the various factors that need to be taken into account for formulating a quality product. Its evaluation is a necessary criterion for determining the value of the final product and hence evaluation parameters were reasoned about. Lastly, the packaging requirements which are of different types and chosen according to the needs were discussed because it has an important role in protecting the product from environmental effects.

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AUTHORS CONTRIBUTION

All authors have taken part in the design and drafting of the article and revising it critically for important intellectual content as well as approval of the final version.

CONFLICT OF INTERESTS

Declared none

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