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A REVIEW ON FAST DISSOLVING SUBLINGUAL FILM FOR SYSTEMIC DRUG DELIVERY

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ABSTRACT

Drug delivery via the oral mucous membrane is considered to be a promising alternative to the oral route. Sublingual meaning is "under the tongue" ,administrating substances via mouth in such way that the substances is rapidly absorbed via blood vessels under tongue .Sublingual route is a rapid onset of action and better patient compliance than orally ingested tablet. The portion of drug absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolism and giving acceptable bioavailability. Orally fast dissolving films are an emerging technology with fast onset of activity and improved patient compliance .These formulation are suitable for cold, allergy rhinitis, asthma attacks, CNS issue where fast onset of activity is needed for quicker help.

INTRODUCTION

Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphasia is a common problem of all age groups, especially, children, and patient who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/ diets have difficulties in swallowing these dosage forms[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 & dissolves in the saliva without the use of water[2].It provides the direct entry into the systemic circulation therapy avoiding the hepatic first pass effect and ease of administration .This delivery system consists of a thin film, is simply place below the tongue, instantly wet by saliva, the film rapidly disintegrates and dissolves to release the medication for systemic absorption . The fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist sublingual environment[3].

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 main mechanism for the absorption of the drug in to oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in oral cavity [1]

Orally fast dissolving film is new drug delivery system for the oral delivery of the drugs .It was developed on the basis of techno of the transdermal patch . The delivery system consist of a very thin oral strip, which is simply placed on the patient tongue or any oral mucosal tissue, instantly wet the saliva tha film rapidly hydrates and adhers onto the site of application . It then rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. Technology catalysts forecasts the market for drug products in oral thin formulation was valued of $500 million in 2007 and could reach $2 billion in 2012. Based on upward global growth trends of the past decade, the fast dissolving dosage market could produce revenues of $13 billion by 2015.

The fast dissolving film is prepared using hydrophilic polymers that rapidly dissolves or disintegrates in the mouth within few seconds and eliminates the fear of chocking as an alternative to fast dissolving tablets [4,5].

Overview of the oral cavity [6]

The target sites for local drug delivery in the oral cavity include the following : Buccal, sublingual , periodontal region, tongue gum. Other desirable targeting sites adjacent to oral cavity pharynx, larynx, adenoids and tonsils. Within the oral cavity, delivery of drugs via the membranes of the oral cavity is classified into three categories.

1)Sublingual delivery

Which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation.

2) Buccal delivery

Which is drug administration through the mucosal membranes lining the cheeks and the area between the gums and upper and lower lips to the systemic circulation.

3) Local delivery

Which is drug delivery to periodontal, gingival delivery for the local treatment of ulcers , bacterial and fungal infection.

Sublingual 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.

Sublingual absorption[7,8]

Sublingual, meaning literally 'under the tongue' refers to a method of administering substances via the mouth. The substances are rapidly absorbed via the blood Vessels under

the tongue rather than via the digestive tract. Impressive absorption has been attained with sublingual administration of desoxycortisone acetate, morphine, captopril, nifedipine and 17-B Oestradio interestingly.

Advantages of film

- Easy of administration to patient who refuse to swallow a tablet, such as pediatric, geriatric patient .
- Water is not required for swallowing the dosage form which is convenient feature gor patient who are travelling and do not have immediate access to water.
- Fast dissolution of medicament and absorption which will leads to rapid onset of action.
- It provides advantages of liquid formulation in the form of solid dosage form.
- Convenience in administration of drug and accurate dosing as compared to liquid formulation.
- Permit continuous drug administration and the use of drug with a short biological half life.
- The first pass effect can be avoided reduction in the dose which can prompt to decrease in side effects associated with the molecule.

Disadvantages of film

- High dose cannot be incorporated.
- Dose uniformity is a technical challenges.
- Although this site is not well suited to sustained delivery system .
- Sublingual medication cannot be used when a patient is unconscious or uncooperative.
- These films are moisture sensitive and expensive packing of oral film is required.

Formulation of fast dissolving film[9,10,11,12]

Mouth dissolving film is a thin film with an area of 5-20 cm2 containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers. A typical composition contains the following:

Table 1: Composition of fast dissolving oral film

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.	Colouring agent	1%

1) Active pharmaceutical agent

The drug selected for oral films should posses good stability in saliva and water with low dose.The film should consist of 1-25%w/w of the drug .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 film.

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

Active Pharmaceutical category	Therapeutic category	Dose
Zolmitriptan	Anti migraine	2.5 mg
Loratidine	Anti histaminic	5-10mg
Dicyclomine	Musle relaxant	25mg
Ketoprofen	Anti inflammatory	12.5-25mg

2. Film forming polymer

The polymer can be used alone or in combination to obtain the desired strip properties. Both natural and synthetic polymer can be used in the formulation of oral film.The polymer should not be very expensive and should be readialy available. In order to prepare a film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. Water dissolvable polymer that may be used include natural gums such as xanthan, guar, acacia, tragacanth other available polymers include cellulose or cellulose derivatives, hydroxypropylmethyl cellulose with different grades like HPMC E15, HPMC E5, HPMC K4M, HPMC K100, hydroxyl ethyl cellulose, hydroxyl propylcelluose, carboxy methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, pullulan, gelatin.

3. Plasticizer

Plasticizer is a key ingredient of the quick dissolving films. Plasticizer serves to enhance the flexibility of the strip and reduces the brittleness of the films. It significantly enhances the film forming properties by diminishing the glass transition temperature of the polymer. Glycerol, propylene glycol, low molecular weight propylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl.

4. Saliva stimulating agent

The purpose of using saliva stimulating agent is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulation. These are used in 2-6%.Example-Citric acid, lactic acid .

5. Sweetening agent

Sweeteners have important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Sweetners used are sucrose, fructose , glucose, isomaltose. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

6. Flavouring agent

Preferably up to 10%w/w flavors are added in the Fast dissolving film formulations The depends on the initial flavor 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. Any flavour can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweetmint, spearmint, wintergreen, cinnamon, clove.

7. Colouring agent

A full range of colour is available including FD&C colour, natural colour, EU colour.Colouring agent used are titanium dioxide, silicon dioxide, zinc oxide.

Manufacturing method[13,14]

There are five method for manufacturing purpose

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

1) Solvent casting method

In this method water soluble are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both the solution are mixed and stirred and finally casted in to the petri plate , dried ,cut in to uniform dimensions.

2) Semi solid casting method

In this method firstly 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.

3) Hot melt extrusion method

In this method firstly 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.

4) Solid dispersion method

In this method immiscible components are extrude with drug and then solid dispersion are prepared. Finally the solid dispersion are shaped in to films .

5) Rolling method

In this 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 roller and cut in to desired shape and sizes.

Evaluation parameter for sublingual film [15, 16, 17, 18, 19 ,20]

1) Film thickness

The thickness of film is directly concern with drug content uniformity so it is necessary to as certain uniformity in the thickness of the film. It can be measured by micrometer gauge or calibrated digital Vernier Caliper at different strategic location.

2) Weight variation

Weight variation is studied by individually weighing 10 randomly selected film and by calculating the average weight.

3) 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

$$\text{Tensile strength} = \frac{\text{Load at Failure x 100}}{\text{Strip thickness x Strip width}}$$

4) Folding endurance

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

5) pH value

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution .It is necessary that film should have nearly uniform Ph value.

6) 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 .

% Elongation = Increase in length x 100 / Original length

7) Uniformity of drug content

This parameter was determined by dissolving one film of dimension 2x2 cm by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking, from this, 10 ml was diluted to 50 ml 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) InVitro dissolution studies

The in vitro dissolution study can be carried out in 500 ml pH 6.8 phosphate buffer using (USP) XIV paddle apparatus II at 370±0.5°C and at50 rpm. Each square cut film sample is submerged into the dissolution media and appropriate aliquots were withdrawn at specific intervals for 30 min. The drug concentration is measured by a UV spectro-photometer.

9) Disintegration time

Disintegration of orally fast dissolving films requires US disintegration appatatus . The disintegration time limit of 30 seconds or less for orally disintegrating tablet described in Centre for Drug Evaluation and Research guideline can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds.

4) Dryness test /tack test

Tack test tenacity with which the strip adheres to an accessory that has been pressed into contact with the strip. Instruments are also available for this study.

CONCLUSION

Fast dissolving sublingual film have gained popularity because of better patient compliance, rapid onset of action .Fast dissolving films are intended to be applied in the mouth and it is a very innovative dosage especially to paediatric and geriatric patients. The drug is directly absorbed into systemic circulation, so drug which undergo the extensive first pass metabolism sublingual route is very useful. Films have several advantages over the conventional dosage form. So they are of great importance during the emergency codition like allergy, short term spasm and asthma a whenever immediate onset of action is required. Therefore sublingual thin film are an accepted for technology for systemic delivery of drugs.

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