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Novel approach towards treatment of Angina pectoris using Nitroglycerin oral thin films

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ABSTRACT
The sublingual route of administration is mostly used now adays due to its effectiveness, easy administration and patient compliance.Some geriatric, pediatric patients find it difficult to swallow capsules and tablets wherein this can prove a beneficial way for the administration of drugs. In some conditions such as coughing, motion sickness, vomiting etc a person may face difficulty to administer tablets and capsules. To overcome these problems, sublingual oral thin films is formed.Angina pectoris is nowadays in many patientsthis occurs when the heart muscles do not receive enough blood. To treat this situation mainly nitroglycerin is used which acts by relaxing and widening blood vessels which can allow the blood to flow properly. The sublingual route is very effective as the drugabsorbs in the sublingual blood vessels and acts quickly. This article reviews the advantages, viewpoints, manufacturing methods and evaluation parameters of the thin films with a wide knowledge of action of Nitroglycerin on angina pectoris.

Key words: Nitroglycerin, Angina pectoris, Sublingual route, oral thin films, myocardial ischemia.

I. INTRODUCTION: -

The most popular oral dosage form are tablets and capsules but many patients find it difficult to swallow tablets and hard gelatin capsules particularly pediatric and geriatric patients. Also, in some cases such as in motion sickness, sudden episode of allergic attack or coughing fear of chocking and swallowing of tablet or capsule may become difficult. To overcome these difficulties several fast-dissolving drug delivery system are developed

To eliminate the drawbacks of conventional dosage form and fast dissolving tablet a fast-dissolving film can be placed. Fast dissolving films are simply placed on patients' tongue or any oral mucosal tissue it instantly wets by saliva and adheres onto site of application. It is then rapidly dissolved and disintegrates to release the medicament which is then absorbed by the oral mucosal membrane. This system is mainly suited for the drugs which undergo high first pass metabolism and is used for improving the bioavailability of the drug

Angina pectoris is a result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand.The common symptoms typically seen are chest pain among patient with coronary artery disease. To treat this nitroglycerin being a powerful vasodilator is used to prevent the chest pain by relaxing the smooth muscle of blood vessels in the heart there by increasing blood flow and oxygen to the heart muscle. This reduction in hearts workload release the pain of angina pectoris

Ideal properties of fast dissolving films: -[3]

- It should be pleasing to mouth and have acceptable taste
- These films should be less fragile and have good mechanical strength
- The drugs incorporated should have a good stability and solubility in water as well as in saliva
- It should be compatible with all the other drugs
- The film should not leave any residue in mouth
- They should quickly dissolve to release the drug instantaneously. [1] [3]

ADVANTAGES: -

- It has rapid onset of action and enhanced stability
- Convenient and accurate dose can be incorporated

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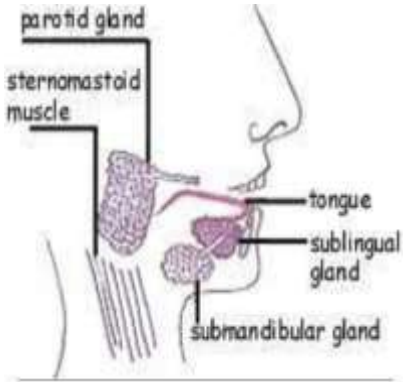
- No risk of chocking with easy handling and transportation
- Improve bioavailability for certain therapeutic ingredients.

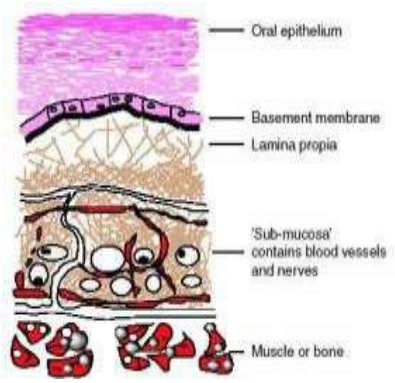
DISADVANTAGES: -[3]

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- Drugs can't be administered if they are unstable at buccal ph.
- Drug in large dose cannot be administered.
- Masking of drugs is needed for drugs having bitter taste
- It takes Special packaging due to fragile in nature and must be protected from water.
- Drugs which are irritate to the mucosa which cannot be administered by this route.

Mechanismof Action of Oral thin film

Sublingual administrated drugs are rapidly absorbed into the reticulated vein, which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, and brachiocephalic vein and are then drained into the systemic circulation. Upon administrating sublingually,the drug reaches directly into the blood stream through the of the tongue and floor of the mouth. The main mechanism for the absorption in oral mucosa is via passive diffusion into the lipoidal membrane. The drug absorption through sublingual route is 3 to 10 times greater than oral route. It can only be surpassed by hypodermic injection.[4]





Action of Nitro-glycerine on Angina Pectoris:

Nitro-glycerine and other organic nitrates exert their effects primarily through venous dilation that reduces left ventricular volume (preload) as well as myocardial-wall tension, reducing oxygen requirements (demand). A smaller dilation of arterioles reduces both peripheral vascular resistance and left ventricular pressure at systole (afterload). Collateral circulation, improvement of regional coronary blood flow to ischemic and alleviation of spasms are facilitated by nitrates.

SL, transmucosal, and IV nitrates are used to manage acute angina attacks. They are useful for treating stable angina, but may be less effective for Prinz metal's angina. IV nitro-glycerine is indicated for the immediate treatment of unstable angina, as well as for long-term therapeutic relief. Oral or buccal tablets, topical ointment, or transdermal patches may be used to prevent anticipated attacks. Long-acting nitrates should be added to a BB or CCB in patients with inadequate symptomatic control.

Severe, sudden headaches are a common side effect of nitrate therapy; often dose-related, they have been reported in up to 82% of patients in placebo-controlled trials. Nearly 10% of patients are unable to tolerate nitrates because of disabling headaches or dizziness. In other patients, headaches are mild-to-moderate in severity and either resolve or diminish in intensity with continued nitrate therapy. Tolerance to nitrates may be avoided by incorporating nitrate-free intervals of 10 to 14 hour. [7]

ORAL FILM FORMULATION

There are different types of ingredients require for the formulation of oral films.

- Drug
- Film forming agent
- Plasticizers
- Flavouring and sweetening agent

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• Surfactant
• Thickener and Stabilizers
• Saliva stimulating agent

Film forming agent: -

It is use as carrier for drug. The physiochemical and nature of film former polymer can be change. The mostly cellulose derivative polymer is use as film former like hydroxypropyl methyl cellulose, hydroxy propyl cellulose and sodium carboxy methyl cellulose in different grade and other i.e., sodium alginate, polyvinyl pyrrolidine, polyethylene glycol. The film should not be damage while handling or during transportation time. The tensile strength is depending on types of polymers and amount of polymer used in film. Mainly hydrophilic polymers are used as film former.[8]

Plasticizers: -

The flexibility of film and the brittleness of the polymer film is improved. The plasticizer to be selected depends on the compatibility with polymer, method of formulation and the nature of solvent. There are many plasticizers use i.e. Propylene Glycol, Glycerol, castor oil, citrates derivatives.[6]

Flavouring and sweetening agent: -

The flavours enhance the acceptance of the formulation and enhance the elegance properties of film. Some flavours i.e. menthol, peppermint, essential oils such as methyl salicylate, eucalyptol, thymol, vanilla, cinnamon etc. Sweeteners use to mask the bad odour and bitter taste of the drugs. Both type of sweeteners is used, natural and synthetic sweeteners i.e. monosaccharide's, disaccharides and polysaccharides such as galactose glucose, mannose, fructose, xylose, ribose, dextrose, maltose, sucrose, sugar, sorbitol, xylitol, mannitol and soluble saccharin salts, saccharin, cyclamate salts, acesulfame-K, Aspartame, Neotame respectively.[5]

Surfactant: -

To enhance the solubility and wetting property of film to get release within a minute surfactant are used. The various surfactants used i.e. benzalkonium chloride, sodium lauryl sulphate, benzathine chloride, tween and poloxamer. Thickener and Stabilizers These are stabilized and enhance the viscosity i.e. xanthan gum, carrageenan and derivatives of cellulose.[2]

Saliva stimulating agent: -

These activate the salivary gland to produce the saliva which helps in rapid disintegration of the film. Some acid used as saliva stimulating agent i.e. ascorbic acid, citric acid, lactic acid, tartaric acid. These agents can be used alone or in combination form between 2 to 6%. [5]

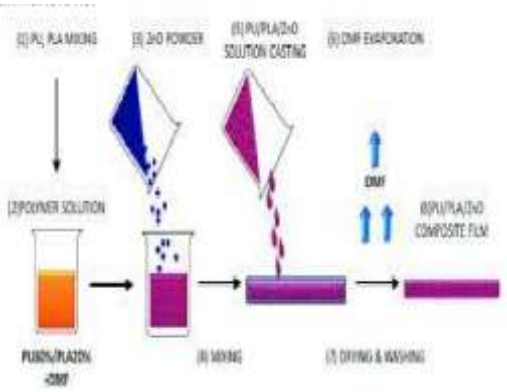
MANUFACTURING METHOD: -

Processes used to manufacture fast dissolving films are: -

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 firstly dissolved in water and then the medicament along with other excipients to be used are dissolved in suitable solvent. Both the solutions are then mixed and stirred and finally casted in to the Petri plate dried and cut in to uniform dimensions.[2]



2. Semi solid casting method: -

In semisolid casting methoda solution of water-soluble film forming polymer is prepared. The resultant solution is added to a solution of acid insoluble polymer (e.g., cellulose acetate phthalate, cellulose acetate butyrate), which was previously prepared in ammonium or sodium hydroxide. After that appropriate amount of plasticizer is added to obtain a gel mass. The gel mass is casted into the films using heat-controlled drums. The thickness of the film is kept about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should not be exceeded than 1:4.[9]

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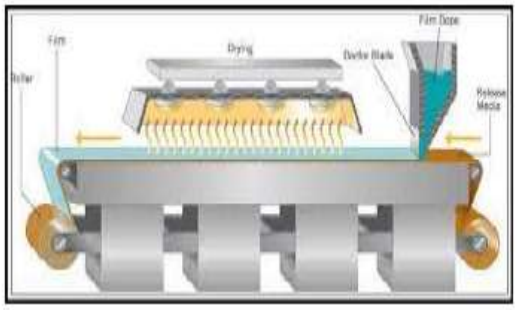
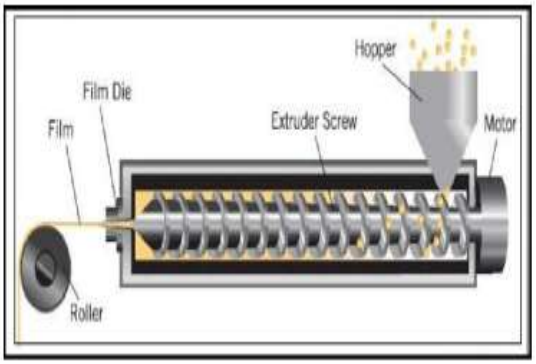


3. Hot melt extrusion method: -

In thismethod,the drug is mixed with carriers in solid form then the extruder having heaters melts the mixture. The melted mixture is then shaped in to films by the dies.

There are certain benefits of hot melt extrusion. · Fewer operation units · Better content uniformity · An anhydrous process. [2]

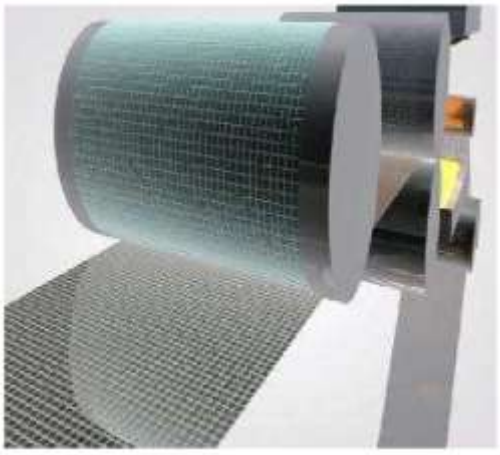


4. Solid dispersion extrusion: -

In solid dispersion extrusionmethod,the different immiscible components are extruded with drug and then solid dispersions are prepared. The solid dispersions are then shaped in to films by means of dies.[9]

5. Rolling method: -

In this method a solution or suspension containing the drug is rolled on a carrier. The solvent is mainly water or mixture of water and alcohol. Then the film is dried on the roller and cut into desired shapes and sizes. [3]



Factors affecting the action of thin film [4]

1. Solubility in salivary secretion: -

The drug should be soluble in aqueous buccal fluids with addition to its high lipid solubility i.e. Absorption requires biphasic solubility of drug.

2. Binding to oral mucosa: -

The systemic availability of drugs binding to oral mucosa is poor.

The drug must have higher lipid solubility as that compare to GI absorption which is necessary for passive permeation for the drug to be completely absorbed.

3. pH and pKa of the saliva: -

As the mean pH of the saliva is 6.0, this pH Favor's the absorption of drugs which remain unionized. if the pKa is greater than 2 for an acid and less than 10 for a base the drug gets absorbed through the oral mucosa.

4. Thickness of the oral epithelium: -

The drug absorption is faster through the sublingual epithelium as its thickness is less compared to the buccal thickness

EVALUATION PARAMETERS

Organoleptic test: [10]

- As the film disintegrates in the oral cavity, it should have acceptable organoleptic characteristics like colour, flavour and taste.
- An oral thin film should have attractive colour as they are administered to children and should be uniform.

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- Flavours used in the formulation should provide good odour and should mask the taste of polymer, drug and other excipients.
- For the process of physical evaluation specially controlled taste panels are used. Specially controlled taste panels have been used for the physical evaluation. Electronic tongue technique is also used which is based on the principle of potentiometric titration method.

Mechanical Properties: -

- Thickness test:

Thickness specifies the dosing accuracy of drug film. It can be measured by a micrometre or screw gauge or calibrated digital Vernier callipers at five different strategic locations and the mean value is calculated which indicates the final thickness of the film. The thickness of the film should be in the range of 5-200 µm.[10]

- Dryness / tack test:

Tack is defined as the tenacity with which the strip gets adhered to an accessory like a piece of paper that has been pressed into contact with strip. Eight stages of film drying process have been identified and these are set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through (dry to handle), dry to recoat and dry print free. Various instruments are available to perform this test. [10]

- Tensile strength:

It is the maximum stress applied to a point of film at which the strip specimen breaks. A film should have good tensile strength. Weight at which the film breaks is known as load failure. Tensile strength is calculated by the applied load at rupture divided by the cross-sectional area of the strip.
Tensile Strength=Load at failure ×100/strip thickness ×strip width [1]

- Percent elongation:

Whenever a stress is applied on the film, it starts stretching and it is called strain. Strain is the deformation of the film divide by the original dimension of the film. It directly depends upon the plasticizer added. As the amount of plasticizer increases, percentage elongation of the film also increases.
% elongation=Increase in length of film×100/Initial length of film. [4]

- Young's modulus:

It is the measure of stiffness of the strip. It is the ratio of applied stress over strain in the region of elastic deformation. Films which are hard and brittle in nature have high tensile strength and young's modulus.
Young's modulus=Slope×100/strip thickness cross × head speed [1]

- Disintegration time: -

Disintegration of orally fast dissolving filmsis measured using USP disintegration apparatus.

According to the CDER guidance the disintegration time for orally disintegrating tablets is of 30 seconds or less can be applied for the fast-dissolving oral films. Disintegrating time will vary depending on the formulation but generally the disintegration ranges from 5 to 30 seconds. for oral fast disintegrating films.[1]

- Surface pH: -

The surface pH of the films is determined by placing the film on the surface of 1.5% w/v agar gel then by immersing pH paper (pH range 1-. 11) on films. The change in the colour of pH paper was observed and reported. [9]

II. CONCLUSION:

Fast dissolving films are mainly used to be applied in the mouth and is a innovative dosageform especially to paediatric and geriatric patients. Sublingual absorption is efficient as the drug absorbed by this route is generally higher than that achieved by oral route. So, oral thin films are an advantageous technology for systemic delivery of API's.This also has greater stability method combine form of the solid and liquid dosage form together making a bridge between two ideas, incorporation of API and excipient in both forms solid and liquid. To treat Angina pectoris mainly nitroglycerin is used which acts by relaxing and widening blood vessels which can allow the blood to flow properly.Nitroglycerinis absorb sublingually fast, and acts quickly at the site of action. So, it can be used in the form oral thin films to treat Angina pectoris. Due to immediate release and ease of manufacturing it can be used in large scale in future.

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