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A REVIEW ON ORAL THIN FILMS FOR SYSTEMIC DRUG DELIVERY

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Abstract:
Oral thin film is novel dosage form of a fast dissolving drug delivery system. Oral thin film administer by sublingual or buccal route. This route is useful when rapid onset of action is required with better patient compliance. The absorption of drug through this route is directly enters into the systemic circulation via venous drainage to the superior venacava. The absorption of drug into the systemic circulation occurs by the passive diffusion, endocytosis or carrier mediated transport. This route is very effective to avoid hepatic first pass metabolism and helps to improve bioavailability. This formulation incorporate low amount of drug load (less than 50 mg) so, it helps in reduction of unwanted side effects. This formulation is required for the patients suffering from heart disease, epilepsy, asthma attack, emesis, migraine or mental disorder. The present article overviews the pharmaceutical factors considered in formulation design and development of oral thin film, such as lipophilicity, solubility, appearance and taste or dosage form, chemical stability and mechanical strength. This review will also focus on the physiological factors that affects the absorption of drug. The absorption of drug may influenced by flow of saliva, pH of the saliva, residence time of the oral thin film, molecular weight of drug and thickness of the oral epithelium.
Keywords: Oral thin film, oral cavity, passive diffusion, endocytosis, lipophilicity,

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INTRODUCTION:

Fast dissolving oral thin film is one of the most important solid dosage form of sublingual and buccal drug delivery system. Oral thin film (OTF) is an ultra- thin film which includes hydrophilic polymer along with active pharmaceutical ingredient and rapidly dissolves in the oral cavity. It sticks or adheres to mucosa when placed on tongue or in the buccal cavity where it dissolves in short period of time when placed in mouth without drinking of water or chewing. Fast dissolving oral thin film are also known as oral thin films, buccal films or strips, oral strips and oral wafer etc.OTF are the most improved form of oral solid dosage form due to more flexibility and comfort of patient.OTF is important and innovative dosage form to improve patient compliance, safety, efficacy and convenience. It has rapidly gained acceptance as an innovative new way of administering drugs. [1]

Drugs which are administered in the oral cavity are generally used to treat local conditions (like local anesthetics for toothaches, oral ulcers, infection, cold sores or teething) or for the systemic absorption of drugs. Oral thin film is placed on the sublingual and buccal mucosal regions which are highly vascularized, so useful for systemic drug delivery. The sublingual and buccal routes are scrutinized promising alternatives to the conventional oral route for drug delivery. OTF gives rapid absorption and instant bioavailability of drugs due to high blood flow at sublingual and buccal region and permeability of oral mucosa is 4-1000 times greater than that of skin.[2]

OTFs are important solid dosage form for the drugs which are potent, which has low molecular weight, poor bioavailability and which undergoes hepatic first pass metabolism. OTFs are beneficial and important in geriatrics, pediatrics, bedridden patients, and the patients who are suffering from vomiting, neurological disorder, migraine, tremors, mental illness. Patient suffering from sudden episode of allergic attacks or patients who are travelling and do not have easy access to water.[10]

Advantages:

- OTF avoids the risk of chocking.
- Rapid onset of action achieved compared to conventional dosage form.
- OTF offers convenience of carrying and administering of dosage form.
- It provides ease of administration of film to the patients suffering from emesis, seizure, mental disorders, migraine and motion sickness.
- OTF avoids the first pass metabolism, so enabling lower drug load to achieve the same therapeutic effect i.e. similar AUC at lower API dosing.
- Avoids destructive acidic environment of stomach.
- Due to lower drug load, it results in reduction of unwanted side effects.
- Provides fast dissolution or disintegration in the oral cavity without need of water or chewing.
- OTF has large surface area for dissolution compared to sublingual tablet.
- OTF offers the convenience of accurate dosing i.e. dose precision.[3]

Disadvantages:

- OTF are limited to highly potent low dose drugs.
- Drugs which gives irritation to mucosa are difficult to administer.
- Taste masking is require for bitter drugs which may reduce maximum drug load for bitter drugs.
- OTF require special packaging due to brittle andhygroscopic nature.
- Sublingual region is continuously washed by saliva which results in drug dilution as well as wash down into GI so, there is need of fast dissolution and quick absorption.[11]
- Sublingual administration of OTF interferes with eating, drinking and talking, so this route is unsuitable for sustained drug delivery system.

Physiology of Oral Cavity:

The oral cavity or mouth is anteriorly delimited by the lips, posteriorly by the oropharynx, superiorly by hard and soft palates and inferiorly by the tongue and floor of the mouth.[5] Oral cavity surrounded by a buccal mucosa that consist of cheeks, along with upper and lower teeth and periodontium. The oral cavity has relatively neutral pH approximately ranges from 6.2 to 7.4 and has limited enzymatic activity.[4]

Structure of Oral Mucosa:

The surface area of the oral mucosa is relatively small approximately 100-200Cm2. Oral mucosa contains three layers as follows:

1) Epithelium: The oral mucosa has an outermost layer made up of stratified squamous epithelium. This cells are similar to other epithelium which present in the whole body. It has a mitotically active basal cell layer, advancing through a number of different middle layers to the superficial layer where

cells are sieve from the surface of the epithelium.[7] The non-keratinized epithelia found to be more permeable to water than keratinized epithelia.

2) Lamina Propia: below the stratified squamous epithelium lies basement membrane, known as lamina propia. It is made up of connective tissue.
3) Sub mucosa Membrane: Sub mucosa membrane consist of connective tissue with a network of blood vessels, lymphatic vessels and smooth muscles.[6]

Components of Oromucousal Region:

1) Oromucousal Cells: Oromucousal cells are made up of carbohydrates and proteins. These cells are adhesive in nature and acts as lubricant and allowing cells to move relative to one another with less friction.[8] The mucous has important role in bioadhesion of oral thin film in mucoadhesive drug delivery system.[9]
2) Salivary Glands: In the oral cavity mucus is secreted by the major and minor salivary glands as part of saliva. There are three types of salivary glands as follows:

a) Parotid gland
b) Submandibular gland
c) Sublingual gland

Saliva contains up to 70% of the total mucin contributed by the minor salivary glands. Saliva contains 99% water and 1% organic and inorganic materials which contains many component of blood plasma. The pH of saliva ranges from 5.5 – 7. The daily salivary volume is 0.5 to 2 liters and this volume is important to dissolve or disintegrate oral thin film.

Oral cavity has four regions given as: buccal, sublingual, gingival and palatal.

a. Buccal region: The surface area of the buccal mucosa 50.2 ± 2.9 Cm2. Buccal region in the oral cavity is lined by non-keratinized stratified squamous epithelium with the membrane thickness of 500 - 800µm and 40 – 50 cells thick in the buccal region. The pH of the buccal mocosa is approximately 6.2 -7.4.
b. Sublingual region: The sublingual mucosa having an estimated surface area of 26.5 ± 4.2 Cm2 and this region in oral cavity are lined by non-keratinized stratified squamous epithelium with the membrane thickness of 100 - 200µm and 40 – 50 cells thick in the sublingual region. The pH of the sublingual region is approximately 6.2 – 7.4.[15]
c. Gingival and palatal region: The mucosa of the gingivae and hard palate are keratinized similar to epidermis which contains ceramides and acylceramides (neutral lipids) which associated with the barrier function. The mucosa of the soft palate have small amount of ceramide which are not keratinized and relatively impermeable to water [7, 9]. They contain small amount of neutral polar lipids. The membrane thickness of palatal region is more than 600µm.[14]

Mechanism of Action of Oral Thin Film:

Oral thin film (fast dissolving drug delivery system) is mostly placed on the patients tongue or any oromucosal tissue.

Drug administer via oral mucosa gain access to systemic circulation through a network of arteries and capillaries. They are richly supplied with blood vessels. Oral thin film immediately wet by saliva due to presence of hydrophilic polymer, so film get rapidly hydrates and dissolves to release the active pharmaceutical ingredient for oromucosal absorption. Drug absorbed in the mucosa drains instantly into blood superior venacava. Drug directly goes into systemic circulation via venous drainage to superior venacava which results in rapid onset of action (short T_{max}). The major artery supplying the blood to the oral cavity is the external carotid artery. This artery supplies blood to the gland and branches to nearing muscles and to mucous membrane of the mouth, tongue and gums. The internal carotid artery supplying blood to the greater part of the cerebral hemisphere. Venous backflow goes through branches of capillaries and veins and finally taken by the jugular vein.

Mechanism of Absorption of Oral Thin Film:

I. Passive Diffusion: Passive diffusion also known as non-ionic diffusion. Passive diffusion involves two types of drug transfer i.e. simple diffusion and filtration or pore transport. In passive diffusion drug is taken up across a sublingual mucosal membrane without need for energy.[19]

- **Simple Diffusion:** This diffusion does not require energy and depends on the difference in concentration of the drug on either side of the membrane. The diffusion generally decreases with increase in molecular weight of the compound. The molecular weight of the most drugs are ranges from 100 – 400D which can be effectively absorbed passively. Both water soluble and fat soluble molecules of small size may cross the membrane by simple diffusion. Drugs which can exist in both ionized and unionized form that offers equilibrium primarily by the transfer of the unionized species; the rate of transfer of unionized species is 3 to 4 times more than the rate for ionized drugs. If the membrane/ water partition coefficient of drug is

increase then increase in rate of absorption. [25]

- **Pore Transport:** It is also known as filtration, bulk flow or convective transport. Pore transport is important in the absorption of drug which has low molecular weight (less than 100). The drug have low molecular size smaller than the diameter of the pore and generally water soluble drugs. The driving force of the filtration is constituted by the hydrostatic pressure or the osmotic differences across the membrane due to which bulk flow of water along with small solid molecules occurs through aqueous channels.

II. **Endocytosis:** In the endocytosis type of absorption, the cells of the oral epithelium and epidermis are able to absorb the drug by endocytosis mechanism. In endocytosis the uptake of solid particles or liquid fluid solutes within a segment of cell membrane to form a vesicle which are usually too large to diffuse through its wall. This mechanism involves engulfing of solid or liquid extracellular material within a segment of cell membrane by forming saccule. This mechanism is important for cellular uptake of macromolecular nutrients like oil soluble vitamins (vitamin A, D, E, and K), fats and mostly lipophilic or hydrophobic drugs. This mechanism is used across the entire stratified epithelium.

III. **Active or Carrier Mediated Transport:** The drug is transported from a region of lower to one of higher concentration. i.e. uphill transport. Endogenous substances are transported actively the use of energy. Carrier mediated transport in which the drug attaches to special "carrier" which facilitates the diffusion of the drug across the membrane and then release the drug. In this mechanism, drug diffuses across the membrane with the help of carrier without change in chemical characteristics of drug. Absorption of some drugs through oral mucosa is increases when carrier pH is lowering (more acidic) and decreases when increase in pH (more alkaline). If more the acidic taste, then greater the stimulation of salivary output, it helps to avoid potential harm to acid- sensitive tooth enamel by showering the mouth in neutralizing fluid. [25]

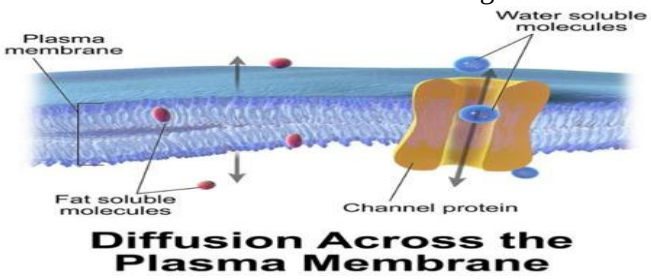

Fig.1 Passive diffusion

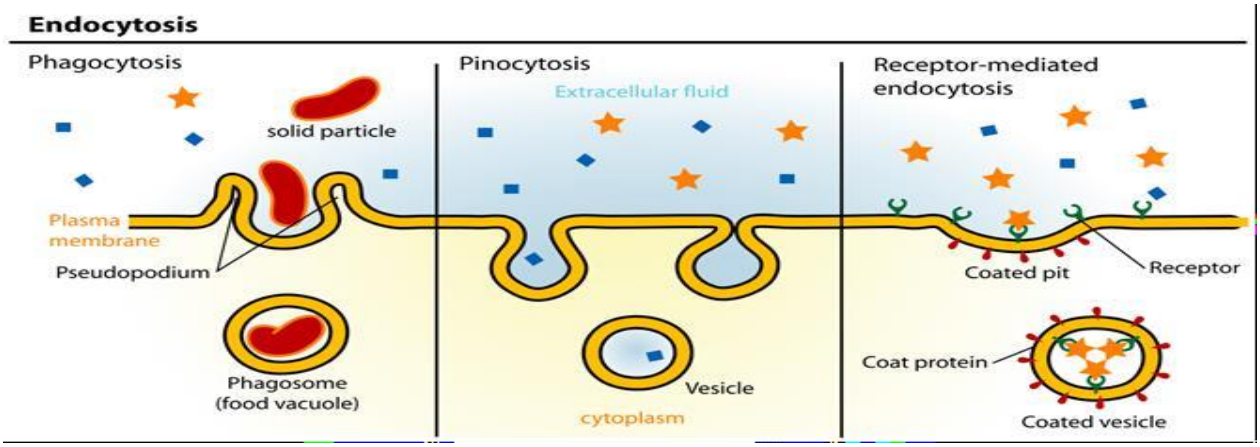

Fig. 2 Endocytosis

Factors Affecting the Absorption of the Drug at the Site of Action: To obtain rapid absorption of the drug from the oral thin film formulation through sublingual or buccal route of administration. There are some physiological factors should be considered in oral thin film formulation design and development. These factors may effect drug bioavailability, efficacy, safety and stability.

1) **Residence Time of Formulation:** Oral thin film placed on sublingual or buccal area. Absorption of the drug is mostly dependent on the residence time of the drug at the site of action. Residence time of the drug is depending on the formulation type and patient. The formulations differ in terms of need for disintegration and dissolution for drug absorption. During the administration of the drug, patients should avoid eating, drinking chewing or swallowing until the medication has been absorbed. Residence time of formulation may increase by using mucoadhesive polymer or hydrophilic polymer [12, 13]. Swallowing of the medication may affect the efficacy of the drug. As increase in residence time of the formulation, it helps to increase the absorption of the drug.[16]
2) **Flow of Saliva:** Flow of saliva may affect the absorption of the drug from oral thin formulation. Saliva flow alters the rate of disintegration of formulation and may affect the dissolution of the drug. If flow of the saliva is very less or mouth is dry, it delays the disintegration of the formulation and dissolution of the drug, so does not obtain rapid onset of action. Saliva flow is increased by using saliva stimulating agents like citric acid, ascorbic acid, tartaric acid or lactic acid etc. Citric acid is mostly preferred as saliva stimulating agent. If saliva flow is more, then this can lead to swallowing of drug before the absorption of it. Flow of saliva may affected by the age, medications and medical conditions of the patient.[17]
3) **pH of the Saliva:** pH of the saliva is most important for the absorption of drug through the sublingual or buccal route of administration. pH of the saliva is important and it ranges from 5.5 to 7.0. Drug absorption is affected by the pH of the saliva by affecting the ionization state of drugs. Oral thin film mostly absorbed by the passive diffusion via transcellular diffusion i.e. through the cell or paracellular i.e. between cells. Passive diffusion is depend on their physicochemical characteristics. In transcellular diffusion, drug passes through the cell, so transcellular diffusion is directly proportional to the lipid solubility of the drug. Lipid solubility of the drug increases when the drug is in the non-ionized form. The non-ionized form of drug is more lipophilic than ionized form, so the drugs with a high pKa value are preferred due to the relatively neutral pH of the saliva. While, in paracellular pathway ionized or hydrophilic drug molecules are preferred for drug absorption. Due to some environmental (e.g. foods and drinks) and personal factors (e.g. oral disease) the pH of the saliva may temporarily altered which can affect the absorption of the drug.[17]
4) **Thickness of Oral Epithelium:** The oral cavity has four regions, which are buccal, sublingual, gingival and palatal. These regions have differences in their thickness of oral epithelium and area for absorption. Thickness of the oral epithelium is inversely proportional to the absorption of drug and directly proportional to the area of absorption. As increase in thickness of the oral epithelium, it decreases absorption of the drug through oral thin film formulation. Thickness of the sublingual region is 100 – 200µm, buccal region is 250 - 300µm while gingival and palatal region is more than 600µm. Buccal region has more area for absorption of drug than the sublingual region.[14,15]
5) **Drug Absorption:** Absorption of drug is affected by the molecular weight of the drug for effective absorption of drug, the drug molecule has balance between its hydrophilic and lipophilic properties, because the drug need to be soluble in aqueous buccal fluids and should also have high lipid solubility to cross the epithelial membrane, by passive diffusion. Absorption of drug through this route is done by the drug molecules which have low to medium molecular weight. Drug absorption can be affected, if the gum or mucosal membrane have inflammation or open sores. This may lead to increase or decrease the absorption of drug. Contrarily, smoking can decrease the absorption of medication due to vasoconstriction of the blood vessels in sublingual or buccal region.[18]

Factors Considering During Formulation of Oral Thin Film:

I. Lipophilicity of Drug: If a drug is to be absorbed from any part of oral cavity, it is necessary for it to pass through cell membranes. Thus, drug must pass through the cells of the mucous membrane of the sublingual or buccal region, and then into the circulation either direct via the capillaries or indirect via the lymphatic channels. Drug should have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation. As cell membranes are lipophilic in nature, the degree and rate of penetration of the drug through them is

dependent to a large extent on the lipid solubility of the drug. Sublingual and buccal region has 4 – 4000 times greater permeability than that of skin. Permeation enhancer are used in formulation of oral thin film, to increase the permeation of drug across the cell membrane. There are some permeation enhancers like aprotinin, benzalkonium chloride, menthol, cyclodextrin etc. are used in formulation of oral thin film. [25]

II. Solubility of drug: During the formulation of oral thin film, solubility of the drug is very important. The drug molecule has balance between its hydrophilic and lipophilic properties, because the drug should able to solubilize in aqueous buccal fluids and also have high lipid solubility to cross the epithelial membrane by passive diffusion. There are many methods by which solubility of drug should be modified. Salt form of drug has more solubility than original form.

III. Appearance of Dosage Form: The appearance of the oral thin film is important for a satisfying compliance by the patient and to avoid the danger of confusion. The appearance of dosage form with color associating with a sweet taste may lead to drug abuse, especially by children. Oral thin film should be free from air bubbles and have smooth, soft and flexible structure. Oral thin film should be free from air bubbles by stirring of solution for long time. The appearance of the oral thin film may improve by the use of different polymers which helps to reduce the recrystallization of the drug in the film during storage.[21] There are some hydrophilic polymers like polyvinyl pyrrolidone, hydroxyl propyl methyl cellulose and methyl cellulose are used in formulation of oral thin film to improve the appearance of it.[20]

IV. Taste of the Dosage form: Taste is most important organoleptic property regarding the evaluation and acceptability of dosage form. As the drug, incorporated in oral thin film, it will partly dissolve in the mouth to interact with the taste receptors.[23] Drug with poor taste may lead to reduced compliance by patient. To improve the taste of the product, effective taste masking is required. Taste masking of the formulation can be carried out by either reduction of the unpleasant taste or by addition of substances to create a favored taste.[20] There are many methods to improve the unpleasant taste of the drug like the addition of sugar alcohols, flavors, nutritive or artificial sweeteners. To improve the taste of oral thin film combination of such excipients are used.[24] E.g. Polyhydric alcohol (sorbitol, mannitol), fructose, sucrose, glucose, saccharine, aspartame, sucralose, neotame etc.

V. Chemical stability: Chemical stability of the drug substance in the saliva is very important for sublingual administration of drug. The drugs which are unstable in saliva, which changes their chemical property which leads to reduce the therapeutic effect. If proteinaceous drugs are used then co-administration of enzyme inhibitors like puromicin, bestatin, aprotinin and bile salts required for inhibition of proteolytic enzymes present in saliva. [25]

VI. Mechanical Strength: Oral thin film should have suitable mechanical strength to resist handling without being damaged mechanical strength of the oral thin film is depend on the selection of the plasticizer. The selection of suitable plasticizer is very important, because sufficient elasticity of films appears beneficial for small scale manufacturing.[22] The impact of unstable plasticizers resulting in brittle films after prolonged storage. The mechanical properties of the oral thin film can be improve by using the combination of polymers in a single formulation. Plasticizers are used to improve mechanical properties of oral thin film along with the tensile strength and elongation. Mechanical properties of the oral thin film is dependent on the concentration of plasticizers. E.g. Glycerol, di-butylpthalate, polyethylene glycol or propylene glycol.

VII. Degree of Ionization: Under physiological conditions some substances are unionized while others are highly ionized. The pH of the saliva is very important to maintain physiological conditions. The ionized and unionized form of drug is depend on pH of the saliva. The mean pH of the saliva is 6.0, at this pH value drug should be in the unionized form. The absorption process is usually proportional to the lipid solubility of the drug. The absorption of unionized molecule is favored because they are more lipid soluble than the ionized form. Ionized form of a drug substance is surrounded by a “shell” of water molecules and is lipid insoluble. The absorption of drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.

CONCLUSION:

Oral thin film is an innovative dosage form for pediatric and geriatric patients. These dosage forms are requiring in immediate or emergency conditions like heart disease, asthma attack, emesis, epileptic seizures or mental disorders. It is also useful in patients who has fear of chocking. These dosage form gives rapid onset of action without hepatic first pass metabolism. This is pain free administration of drug and gives immediate action in low amount of drug which helps to reduced unwanted side effects of it. In the formulation design and development of oral thin film lipophilicity, degree of ionization and solubility

of drug is very important. Residence time of the oral thin film, pH of the saliva, flow of the saliva and thickness of the oral epithelium may affect the absorption of drug and its therapeutic effect.

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