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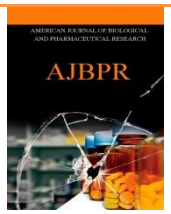

FAST DISSOLVING STRIPS: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Fast dissolving oral drug delivery system are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or chewing. More recently, fast dissolving strips are gaining interest as an alternative to fast dissolving tablets to definitely eliminate patient's fear of chocking and also for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid dosage forms. This technology has been used for local action, rapid release products. The oral strips are formulated using polymers, plasticizer, flavours, colors and sweeteners.

INTRODUCTION

Background

Oral route of administration is the most convenient and preferred route of administration among the various other delivery system. More than 70% of drugs are available in the market in the form of oral drug delivery system due to pain avoidance and versatility. Dysphagia is commonly found among all age groups [1]. Recent development in the technology produce viable dosage alternative to oral route for the pediatric, geriatric, bedridden, nauseous or noncompliant patients. Conventationl tablet formulation are acquired the 50to 60 % market in medicine, according to this data the tablet formulation most popular form but with this tablet having acceptance problem in the patients suffering from dysphagia, Parkinson's disease, mycosystis or vomiting, geriatric, bed ridden, psychotics and pediatric patient due to unwilling to take solid preparations due to fear of choking. Even with the fast dissolving tablet they having chocking problem due to their tablet appearance. According to survey out of 100 patient 26 patient are not acceptable tablet due to their swallowing disability, tablet size, surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as traveling patients who may not have ready access to water. This is largely as a result of the success of the consumer breath freshener product such as Listerine pocket packs in the US consumer market [2].

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CLASSIFICATION OF FAST DISSOLVES TECHNOLOGY

For ease of description, fast-dissolve technologies can be divided in to three broad groups:

Lyophilized systems, Compressed tablet-based systems and thin film strips

The lyophilized systems

The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems [3].

Compressed tablet-based systems:

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard HDPE bottles or blisters through to more special pack designs for product protection. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or superdisintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail.s Fuisz technology. It uses the proprietary Shear form system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms [4].

Thin film strips

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to tablets, capsules and syrups for people experiencing difficulty in swallowing traditional solid dosage forms. This new and novel oral drug delivery system dissolves or disperses quickly in few seconds after placement in the mouth without water can alleviate the problem of swallowing tablets.[4]This fast dissolving system includes tablets, caplets, granules, films, wafers and powders. MDFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices .MDFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs. Fast-dissolving dosage technologies are important for patients who have difficulty taking traditional oral dosage forms, as well as those who want the convenience of any-time dosage when water is not available. Many paediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. The most common complaint was tablet size, followed by larger surface area and taste. For the last two decades, there has been increase use of more patient - compliant dosage forms [5,6].

Fast Dissolving Film

Definition

Mouth dissolving films 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 onto the site of application. It is then rapidly disintegrates and dissolves to release the medication for oromucosal absorption.

Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolve/disintegrate in the mouth within few seconds without water and eliminates the fear of chocking as an alternative to fast dissolving tablets. Most fast dissolving films are having taste masked active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipients. These films generally dissolve within seconds to release the active agents but can be modified to release the drug more slowly depending upon film thickness and selection of the polymer matrix. A film or strip can be defined as a dosage form that employs water. Dissolving polymer which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or in the oral cavity to provide rapid local or systemic drug delivery. Zengen Inc developed this new delivery technology, which is a medicated oral strip structured as a proprietary bilayer system. These films typically contain water soluble hydrocolloids such as HPMC, pullulan, pectin, carboxymethyl cellulose, an effective dose of active agent, other additives such as flavouring agents, plasticizers and preservatives. [6] The disintegration and dissolution characteristic of thin film is dependent on thickness and combination of hydrocolloids. These four tastes are located on different receptors on tongue, sensations for sweet are located at tip of the tongue and sensations for sour are located at sides of the tongue whereas bitterness at the back of the tongue and salty sensations are located at the sides and tip of the tongue. [6]
Among various approaches two are commonly used to diminish the bitter taste of drug:

1. By reducing the solubility of drug in the pH of saliva (pH-5.6-6.8).
2. By altering the affinity and nature of drug which will interact with the taste receptor.

The Rapidly dissolving film are essentially prepared using water soluble and fast disintegrating polymers which also possess good film forming properties like hydroxypropyl methylcellulose (HPMC), Pullulan , polyethylene oxide (PEO),polyvinyl pyrolidone (PVP) and hydroxypropylcellulose (HPC).

Threshold for taste is a minimum conc. Of a substance that evokes perception of taste. It is observed that tounge is 10,000 times more sensitive to the bitterness of quinine than to sweetness of sugar. Taste buds are onion-shaped structures containing between 50 to 100 taste cells. Chemicals from food or oral ingested mendicants are dissolved by the saliva and enter via the taste pore. There they either interact with surface proteins known as taste receptors or with pore-like proteins called ion channels. Salt and sour responses are of the ion channel type of responses, while sweet and bitter are surface protein responses.

Ideal Properties of Fast Dissolving Films [7].

- ✓ It should have an acceptable taste.
- ✓ It should give a pleasing mouth feel.
- ✓ It should be less friable and have good mechanical strength to withstand the post manufacturing handling.
- ✓ It should be stable in environmental conditions.
- ✓ Subsequent to oral administration, it should leave least or no residue in mouth.
- ✓ It should quickly dissolve to release drug instantaneously in mouth.
- ✓ It should be compatible with the other ingredients.

Advantages of Oral FDDDs [8]

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. The disadvantage of most ODT is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.
3. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
4. Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring device.
5. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and canenter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect.
6. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
7. Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
8. OTFs are typically the size of a postage stamp and disintegrate on a patient ís tongue in a matter of seconds for the rapid release of one or more APIs. The formulation of dissolvable films is customarily facilitated through aqueous polymer matrices that span a wide molecular weight (MW) range, thereby providing flexibility to achieve certain physical properties.

Disadvantage of Oral Strip [8].

1. The disadvantage of OS is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-XÆ thin strip has a loading of 62.5 mg of simethicone per strip. There remain a number of technical limitations with the use of film strips.
2. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly limits the range of compatible drug products.
3. The other technical challenge with these dosage forms is achieving Dose Uniformity.

Special Feature of Fast Dissolving Oral Film [9].

- Available in various size and shape
- Thin elegant film
- Un-obstructive
- Fast disintegration or dissolution
- Rapid release

Classification of Oral Films

There are three different subtypes of oral films:

COMPOSITION OF THE SYSTEM

Drugs

A number of molecules can be incorporated into this delivery system. They may include cough/cold remedies (antitussives, expectorants), sore throat, erectile dysfunction drugs, antihistamines, antiasthmatics, gastrointestinal disorders, nausea, pain and CNS (e.g. anti-Parkinsonís disease). Other applications comprise caffeine strips, snoring aid, multivitamins, sleeping aid etc. The OS technology has the potential for delivery of variety of APIs [10].

Ideal Characteristics of a Suitable Drug Candidate

- ➢ The drug should have pleasant taste.

- Dose should be low as possible.
- The drugs with smaller and moderate molecular weight are preferable.
- Good stability in water and saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Water Soluble Polymers

Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application.

The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases.

Ideal Property of Film Forming Polymer

- It should be non-toxic and non irritant, non incompatible and devoid of leachable impurities
- Polymer must be hydrophilic.
- It should have excellent film forming capacity.
- It should have good wetting and spread ability property.
- Polymer should be readily available & should not be very expensive.
- Polymer should have low molecular weight.
- It should have sufficient shelf-life.
- Polymer must be tasteless, colorless.
- It should not cause any secondary infection in oralmucosa.
- It should exhibit adequate peel, shear and tensile strengths

Plasticizers

Formulation considerations have been reported as plasticizer is important factors that affecting on mechanical properties of films. The mechanical properties such as

1. Tensile strength and
2. Elongation

The films has also been improved by the addition of plasticizers. It is Used in 1-20 %w/w of the dry polymer weigh. Their concentration may affect these properties. Low molecular weight of polyethylene glycol was found to better plasticizer than high M.W polyethylene glycol.

Saliva Stimulating Agents

The saliva stimulating agents are enhance, production of saliva that would aid in the faster disintegration of the rapid dissolving film formulations and utilized as salivary stimulants.

These agents are used in combination between 2 to 6%w/w of weight of the strip. Sweeteners are also act as salivary stimulants.

Surfactants

Surfactants are used as solubilising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are: Sodium lauryl sulphate, benzalkonium chloride, bezthonium chloride, tweens etc.

Most important surfactant is polaxamer407 that is used as solubilizing, wetting and dispersing agent.

Flavour

Any flavour can be added, such as intense mints, sour fruit flavours or sweet confectionery flavours.

Natural Flavours

Synthetic Flavours

- Alcoholic solutions
- Aqueous solutions
- Powders

Sweeteners

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination.

Natural Sweetener

Exa: Sucrose, glucose, fructose, Sorbitol, mannitol, glycerol, Honey, liquorice

Artificial Sweetener

Exa: Saccharin, Saccharin sodium, Aspartame

- Nutritive: Sucrose, Fructose and Glucose
- Polyols: Mannitol, Sorbitol, Xylitol, Erythritol, Maltitol.
- Non-Nutritive: Aspartame, Sucralose, Neotame and Saccharine
- Novel sweeteners: Trehalose, Tagatose

Mechanism of Fast Dissolution in Mouth

The delivery system is simply placed on a patient's tongue or any oromucosal tissue. Instantly wet by saliva due to presence of hydrophilic polymer and other excipients, the film rapidly hydrates and dissolves to release the medication for oromucosal absorption.

The name "fast dissolving" indicates that these dosage forms dissolves quickly and disintegrates into smaller particles by saliva and swallowed into the stomach.

The time to reach from mouth to the stomach is estimated to be between 5 and 10 minutes. Hence fast dissolving drug delivery system has the advantage of liquid dosage form i.e. convenient drug administration. The fast passage of dissolved dosage form to the stomach provides a better opportunity for the medication to be absorbed through the membrane of the buccal cavity, pharynx and esophagus for improved bioavailability and quick onset of drug action [11].

Various Technologies Used in Oral Film Formulation and Marketed products of fast dissolving film

XGel

XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

Soluleaves

This is applied to flavour-release products such as mouth fresheners, confectionery and vitamin products. Soluleaves technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form.

Wafertab

Wafertab is a patented delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting.

Foamburst

Foamburst is a new patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt-in-themouth sensation.

Micap:

Micap plc signed an option agreement in 2004 to combine its expertise in micro encapsulation technology with the BioProgress water-soluble films. The developments will be aimed at providing new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs).s

Marketed products of fast dissolving film

ORAL CAVITY

Anatomy of oral cavity

Oral cavity offers a unique environment for delivering the drugs. The oral mucosa allows direct access of drug to the systemic circulation and avoids first pass metabolism. The epithelium of the oral cavity is quite similar to that ofthe skin, with slight differences with regard to keratinization, protective and lubricant mucous which is spread across its surface. The permeability of oral mucosa is 4–1000 times greater than that of the skin. The oral cavity is divided into two regions: outer being the oral vestibule bounded by the lips and cheeks; the hard and soft palates, the floor of the mouth and tonsils [12,13].

Oral Mucosa

The oral cavity on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage , and the virtual lack of langerhans cells makes the oral mucosa tolerant to potential allergies. Furthermore, oral transmucosal drug delivery bye pass first pass effect and avoids pre-systemic elimination in the gastro intestinal tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery . Within the oral mucosal cavity, delivery of drugs is classified into three categories [14].

i). Sublingual delivery which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.

ii). Buccal delivery which is drug administration through mucosal membra ne lining the cheeks (buccal mucosa) and,

iii). Local delivery which is drug delivery into the oral cavity.

The oral mucosa is the "skin " inside the mouth, and it covers most of the oral cavity apart from the teeth.

Function of oral mucosa

The oral mucosa has several functions. Its main purpose is to act as a barrier. It protects the deeper tissues such as fat, muscle, nerve and blood supplies from mechanical insults, such as trauma during chewing, and also prevents the entry of bacteria and some toxic substances into the body [15].

The oral mucosa has an extensive innervation of nerves, which allows the mouth to be very receptive of hot and cold, as well as touch. Taste buds are also located in oral mucosa and are important for recognition of taste.

The major secretion associated with the oral mucosa is saliva, produced by the salivary glands. The major salivary glands secrete most of the saliva via ducts that pass through the oral mucosa. There is a degree of permeability that allows for rapid absorption into the body in certain circumstances.

Composition of oral mucosa [16]

The oral cavitiy is lined by a mu*cous membrane that consists of* mucosa and sub mucosa. Mucosa is consist of Epithelium Lamina propria

1. Mucosa:

A) Epithelium:

Oral epithelium forms the surface of the oral mucosa that forms a barrier between the oral environment and the deeper tissues. It is derived from the embryonic ectoderm.It is stratified squamous epithelium and may or may not be keratinized. Beneath the epithelium lies the connective tissue. The oral mucosa is composed of an outermost layer of stratified squamous epithelium. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. composition of the epithelium also varies depending on the site in the oral cavity.

Keratinized oral epithelium

Most of oral mucosal surface is lined by non Keratinized stratified squamous epithelium except gingival, hard palate and dorsal surface of the tounge where the epithelium is Keratinized. The Keratinized cell have no nuclei and the cytoplasm is displaced by large numbers of keratin filaments. Keratinized epithelium is associated with mastcatory function and have four layers of cells.

The four layers are:

1. Stratum basale
2. Stratum Spinosum
3. Stratum Granulosum
4. Stratum Corneum

Nonkeratinized oral epithelium

Nonkeratinized oral epithelium cells in the superficial layers do not have keratin filaments in the cytoplasm. The surface cell also have nuclei. The stratum corneum and stratum granulosum layers are absent. The epithelium is associated with linning of oral cavity.

B) lamina propria

- lamina propria is the Connective tissue layer immediately below the epithelium.
- It can be divided into papillary layer and reticular layer.
- papillary layer forms finger like projections of Connective tissue that extend deep in the epithelial layers.
- papillary layer is prominent in masticatory mucosa and reticular layer is prominent in linning mucoasa.
- lamina propria consist of blood vessels and cell like fibroblasts, cell of blood vessels, and lymphatics and nerves.
- Epithelim is avascular, hence its metabolic needs come via the vessels of the lamina propria.

C) **The Submucosa as the innermost layer.**

Submucosa lies below lamina propria and serves as an attachment between lamina propria and bone or skeletal muscles. It is found in the cheeks, lips, and parts of the palate. It consists of large vessels, nerves and lymphatics and its function are nutrition and defence.

Permeability of oral mucosa

The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeabilityof the buccal mucosa is 4-4000 times greater than that of the skin. There are considerable differences in permeability between different regions of the oral cavity different oral mucosa. For the better absorption of APIs in oral region permeation enhancer play important role. So if we want to absorb the drug mostly in mouth as drug released from formulation then there is the need of permeation enhancer.

Some example of permeation enhancer given;

- 23-lauryl ether
- Azone
- Benzalkonium chloride
- Cetylpyridinium chloride
- Cyclodextrin
- Dextran sulfate
- Menthol
- Sodium glycodeoxycholate
- Sodium taurodeoxycholate
- Aprotinin

Composition of Oromucosal Region

Oromucosal Cells

Oromucosal Cells Are made up of proteins and carbohydrates. It is adhesive in nature and acts as lubricant, allowing cells to move relative to one another with less friction . The mucus is also believed to play a role in bioadhesion of mucoadhesive drug deliverysy stems. In other part of body mucus is synthesized and secreted by the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands.

Another feature of the oral cavity is the presence of saliva (digestive secretion) produced by three pairs of salivary glands (parotid, submandibular and sublingual glands). Saliva is mostly water with 1% organic and norganic materials. The digestive enzyme present insaliva is salivary amylase, which breaks down starch molecules to shorter chains of glucose molecules. Saliva is made from blood plasma and thus contains many of the chemicals that are found in plasma. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus and the degree of stimulation . The salivary pH ranges from 5.5 to 7. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral

mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

The turnover time for the buccal epithelium has been estimated at 5-6 days and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingivae measure at about 100-200 µm. The The mucosae of the gingivae and hard palate are keratinized similar to the epidermis which containe ceramides and acylceramides (neutral lipids)which have been associated with the barrier function. The mucosa of the soft palate, the sublingual and the buccal regions, however, are not keratinized which are relatively impermeable to water and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. The nonkeratinized epithelia have been found to be considerably more permeable to water than keratinizedepithelia.

Tongue

Mucosa of the Tongue

Specialized mucosa covers the dorsal surface of the body of tongue. The connective tissue binds the epithelium to the underlying skeletal muscle. The epithelium is modified, keratinized, stratified covered with papillae, which can be seen by naked eye.

- Dorsum of the Tongue
- Median Sulcus:
- Ventral Surface of the Tongue:
- Apex of the Tongue
- Papillae:

Dorsum of the Tongue: Superior (top) surface of the tongue.

Median Sulcus: A centralized linear indentation on the dorsum of the tongue running anterior to posterior.

Ventral Surface of the Tongue: Inferior (underneath) surface of the tongue. The ventral surface of the tongue is very vascular and covered with thin, alveolar mucosa.

Apex of the Tongue: Anterior tip of the tongue.

Papillae:

The different papillae on the dorsal surface of the tongue are:

1. Filliform papillae
2. Fungiform Papillae
3. Circumvallate Papillae
4. Foliate papillae

1. Filli form papillae: Filli form papillae are pointed extensions of the keratinized apithelial cells. They are the most numerous papillae of the tongue. They are not associated with taste buds. Small cone shaped papillae found in the anterior 2/3 of the dorsum that are responsible for the sense of touch [17].

2. Fungiform Papillae: Fungi form Papillae are fewer than the Fillii form Papillae and are scattered over the dorsal surface of the tongue. They are rounded elevations above the surface of the tongue. They have taste buds on their superior surfaces. The surface of fungiform papillae is not keratinized. Mushroom-shaped papillae spread evenly over the entire dorsum of the tongue. They are deep red in color and each contains a taste bud.

3. Circumvallate Papillae: the Circumvallate Papillae are located at the junction of the anterior two thirds (body) and one third (base) of the tongue. There are eight to twelve in number and bigger than fungi form papillae. Circumvallate Papillae are lined with taste buds and also opening of serous glands. Cup-shaped papillae that are approximately 1-2 mm wide and found on the posterior dorsum of the tongue. They are usually arranged in 2 rows that form a "V-shape". Each papilla contains a taste bud.[17]

Evaluation of the Fast Dissolving Strips: [18-20]

• Mechanical properties

- Thickness
- Dryness/ tacktest
- Tensile strength
- Percent elongation
- Young's modulus
- Tear resistance
- Folding endurance

Organoleptic test

Swelling test

• Surface pH test
• Contact angle
• Transparency
• Assay/ content uniformity
• Disintegration test
• In-vitro diffusion test

Stability study

Weight of Films

Mouth dissolving films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API [21,22].

Thickness

A thickness of film should be measured with the help of micrometer screw gauge or calibrated digital verniercallipers. Film should be measured at five points i.e. from the centre and from all the four corners and then mean

thickness is calculated. It is necessary to determine the uniformity of thickness as it is directly related to accuracy of dose in the film [23].

Dryness/ Tack test

Dryness is the property to measure the solvent or water content present in the film whereas tack is the tenacity with which the film adheres to any piece of paper which is pressed into contact with the strip. Eight stages of film drying process have been recognized i.e. set-to-touch, dust-free, tack-free, dry-to-touch, dry-hard, dry-through; dry-to-recoat & dry print free. Now instruments are also available to study [23,24].

Tensile strength

It is the maximum stress applied to a point of a film at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross section area of the strip as given in the equation:

Tensile strength= Load at failure*100/ strip thickness* strip width [24,25]

Percent Elongation

When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increases [26].

Percent elongation= $L*100/L_o$

L = Increase in length of film

L_o = Initial length of film

Young's Modulus:

Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's Modulus= Slope*100/ Film thickness* cross head speed

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation [25-27].

Tear Resistance:

The maximum stress or force (that is generally found near the onset of tearing) required to tear the film is recorded as the tear resistance value in Newton (or pounds -force) [20,21].

Folding Endurance:.

Folding endurance is determined by repeated folding of the film at the same place till the fill breaks. The number of times the film is folded without breaking is computed as the folding endurance value. [23,24]

Organoleptic Evaluation:

This is essential step in case of most oral formulation due to more residence time in the oral cavity. The product should possess the desired features of sweetness and flavour which is acceptable to large mass of population. For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. Experiments using electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste masking formulation [25,26].

Swelling Test

Simulated saliva solution is used to conduct the swelling property study. Firstly weigh all the samples of film and placed on the preweighed stainless steel wire mesh. 15ml of the saliva solution is added in the plastic container and the mesh containing film sample is submerged into it. Increase in weight of film was observed until a constant weight was observed. The degree of swelling was calculated using parameters:

$\alpha = w_t - w_o / w_o$

w_t = weight of film at time t

w_o= weight of film at time zero [27,28]

- **Surface pH Test:**

The pH value was determined by dissolving film in 10 ml distilled water and the pH of the obtained solution was measured. All determinations were performed in triplicate. It is necessary that film should have nearly uniform pH value.

Contact Angle

Contact angle are measured by Goniometer (AB Lorentz and wettre, Germany) at room temperature. Take a dry film and place a drop of distilled water on the surface of the dry film. Images of water droplet were recorded with in 10 sec of deposition by means of digital camera. The contact angle was measured on both side of drop and average is taken.

Transparency

The transparency of the film scan be determined using a simple UV spectrophotometer. Cut the film in the rectangular shape and placed inside the spectrophotometer cell. Determine the transparency of the film at 600nm.The transparency of the film was calculated as follows:

Transparency= (log T600)/b = —єC

Where, T600= transmittance at 600nm, b= film thickness (mm), C= concentration

Assay/ Content Uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by

estimating the API content in individual strip. Limit of content uniformity is 85-115%.

Disintegration Test

The disintegration time limit is 90sec or less. Although no official guidelines is available for oral strips. Pharmacopoeial disintegrating test apparatus may be used for the study. Typical disintegration time for oral strip is 5-30sec. USP disintegration apparatus can be used to study disintegration time. In another method, the disintegration time can be visually determined by dipping the strip in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film start to break or disintegrates.

In-vitro Diffusion test: In Vitro Diffusion study through cellophane membrane carried out using the Franz diffusion cell. Cellophane membrane was mounted between donor and receptor compartments. Receptor compartment was filled with stimulated salivary fluid pH 6.8 and hydrodynamics was maintained using magnetic stirrer. One film of dimension 3*3 cm (9 cme2) was previously moistened with few drop of stimulated salivary fluid pH 6.8. and placed in donor compartment. Donor compartment was filled with 1 ml stimulated salivary fluid pH 6.8. 2 ml sample from receptor compartment were withdrawn at suitable time interval which was then replaced with 2 ml stimulated salivary fluid pH 6.8.

Stability Studies

Stability studies on the optimized formulation of mouth dissolving film were carried out to determine the effect of temperature and humidity on the stability of the drug. The film (optimized batch M1) was stored in stability chamber at 40°C/75%RH, and 25°C/40%RH. The sample were withdrawn at 90 days and subjected for disintegration test and in vitro dissolution studies to determine disintegration time and cumulative % drug release [28].

Table 1. Classification of oral films

Property/sub type	Flash release wafer	Mucoadhesive melt-away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4
Thickness(µm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer System	Multi-layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue (upperpalate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 sec	Disintegration in a few min forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Table 2. List of drugs use in fast dissolving oral film/strips

Drug	Dose	Therapeutic class
Chlorpheniramine maleate	4mg	Anti-allergic
Triplolidine hydrochloride	2.5mg	Anti-histaminic
Loperamide	2mg	Anti diarrhoeal
Famotidine	10mg	Antacid
Azatidine maleate	1mg	Anti-histaminic
Sumatriptan succinate	35-70 mg	Anti-migraine
Ketoprofen	12.5 Mg	Analgesic

Table 3. Type of polymers

Natural Polymers	Synthetic Polymers
Pullulan	Hydroxyl propyl methyl cellulose (hypromellose)
Gelatine	Polyvinyl pyrrolidone(PVP)
Modified starches	Polyvinyl alcohol
xanthan gum	Polyethylene oxide
locust bean gum	Low viscocity grade HPC
guar gum	sodium carboxymethyl cellulose
Carrageenan	hydroxyl ethyl cellulose

Table 4. Examples of plasticizers

Glycerol	Polyethylene glycol
Dimethylpthalate	Castor oil
Diethylpthalate	Glycerine
Dibutylpthalate	Propylene glycol

Table 5. Examples of Saliva Stimulating Agents

Citric acid	Malic acid
Ascorbic acid	Tartaric acid

Table 6. Examples of Natural Flavours

Juices	Raspberry
Extracts	Liquorices
Spirits	Lemon & Orange
Syrups	Blackcurrant
Tinctures	Ginger
Aromatic waters	Anise & Cinnamon
Aromatic Oils	Peppermint & Lemon

Table 7. List of masking agent

Basic taste	Masking agents
Salt	Butterscotch, maple, apricot,peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry
Sour	Citrus flavor, licorice, root beer, raspberry.

Table 8. Marketed products of fast dissolving film

Brand name	Manufacturer/ Distributor	API (strength)	Uses
Klonopin Wafers	Solvay Pharmaceuticals	Clonazepam (strengths:0.125mg,0.25mg, 0.5mg, 1mg and 2mg.)	Treatment of Anxiety
Listerine Cool Mint	Pfizer, Inc	Cool mint	Mouth Fresheners
Sudafed PE	Wolters Kluwer Health,Inc.	Phenylephrine	Relieving Congestion
Suppress®.	InnoZen®, Inc	Menthol (2.5 mg)	Cough Suppressants
Triaminic	Novartis	Diphenhydramine HCL (12.5 mg)	Anti-allergic
Theraflu	Novartis	Dextromethorphan HBR(15 mg)	Cough Suppressants
Orajel	Del	Menthol/pectin (2mg/30mg)	Mouth ulcer
Gas-X	Novartis	Simethicone (62.5mg)	Anti Flatuating
Chloraseptic	Prestige	Benzocaine/menthol(3mg/3mg)	Sore throat
Benadryl	Pfizer	Diphenyhdramine HCl (12.5mg or 25mg)	Anti-allergic

Table 9. Type of oral mucosa

Region	Epithelium	Lamina propria	Submucosa
Soft Palate	Thin, nonkeratinized; taste buds present	Thick with numerous short papillae	Loose connective tissue; minor salivary glands
Ventral Tongue	Thin, nonkeratinized	Thin with short papillae; extensive capillary network	Thin and irregular
Floor of Mouth	Very thin, nonkeratinized	Short papillae; Extensivevascular supply	Loose connective tissue
Alveolar Mucosa	Thin, nonkeratinized	Short papillae	Loose connective tissue containing elastic fibers

Labial & Buccal Mucosa	Very thick, nonkeratinized	Long slender papillae but wide rete ridges, dense connective tissue with elastic fibers	Mucosa attached to underlying muscle; minor salivary glands
Vermillion Zone	Thin, keratinized	Numerous papillae and extensive capillaries	Mucosa attached to underlying muscle
Gingiva	Thick, ortho- or parakeratinized epithelium	Long, narrow papillae and rete ridges, dense connective tissue	Mucoperiosteum
Hard Palate	Thick, ortho- or parakeratinized epithelium	Long, narrow papillae, dense connective tissue	Mucoperiosteum, except over neurovascular bundles in posterior lateral region; minor salivary glands

Figure 1. Anatomy of oral cavity

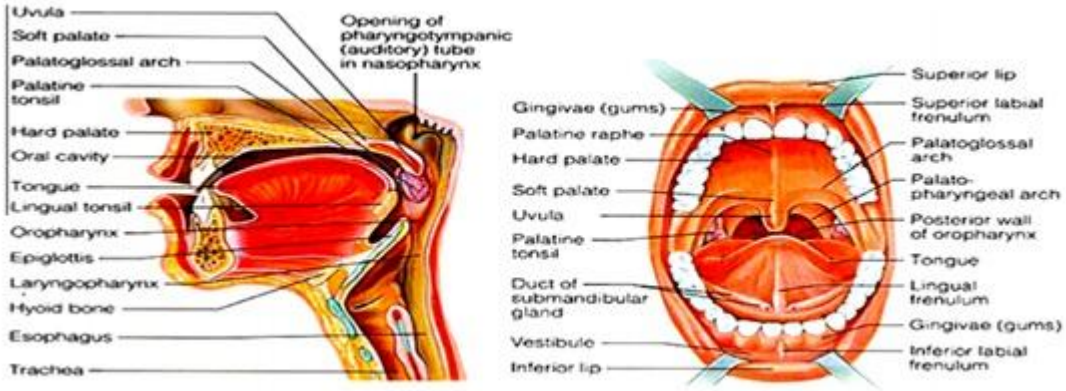


Figure 2. Structure of Oral Mucosa membrane

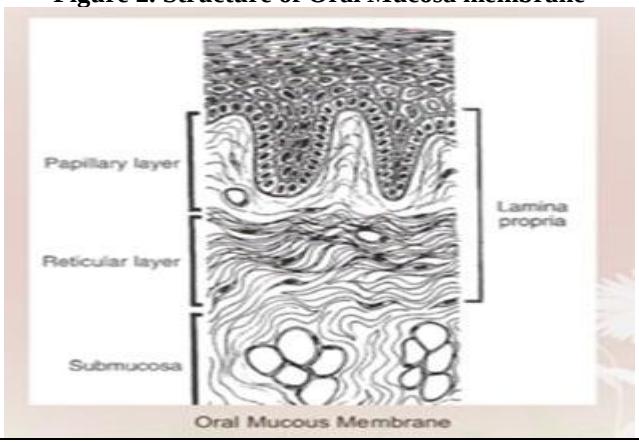
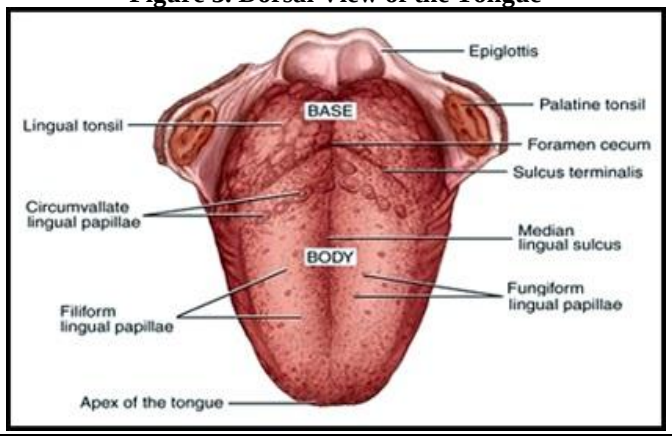


Figure 3. Dorsal View of the Tongue



CONCLUSION

The growing success and popularity of fast dissolving oral strip recently in global market is evidence to the need for effective taste masked, "without water" pharmaceutical formulations. Fast dissolving oral strips being a natural evolution of fast dissolving drug delivery systems have prominent advantages over conventional dosage forms and orally disintegrating tablets. Due to their immense importance during the emergency cases such as allergic reactions and high patient compliance, fast dissolving oral strips have evolved as consumer friendly dosage forms. So many of the pharmaceutical companies are launching this technology as these strips can be manufactured through non-sophisticated, uncomplicated equipment and procedures. Due to these, fast dissolving strips have economically feasible developmental futuristic opportunities.

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