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A MODERN EXPANSION IN DRUG DELIVERY SYSTEM OF MOUTH DISSOLVING STRIP

R. Ajith Kumar* and Dr. K. Sundharamoorthy

Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur, Tamil Nadu-603319, India.

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***Corresponding Author**
R. Ajith Kumar
Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur, Tamil Nadu-603319, India.

ABSTRACT

The aim of Novel Drug Delivery System is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug content. A number of novel drug delivery system has emerged encompassing various routes of administration, to achieve desired pharmacological effect. Oral route of administration is the most preferred route, Mouth dissolving strip has benefits like self administration, no water required for swallowing, no risk of chocking, rapidly acting medications that are poorly water soluble that dissolves and absorbs rapidly, improved oral absorption and bioavailability of the drug. Mouth dissolving strip is an innovative drug delivery technology which can provide solution for the disadvantages of liquid dosage forms and bring together with the advantages of solid dosage form. Mouth dissolving strip is a unique thin postage stamp sized dosage form required to be placed on the tongue, where it will be disintegrate immediately by absorbing saliva without need of water and will turn into a suspension or a solution which will be easily swallowed by children. This review is focusing on the formulation, evaluation, characteristics and application of mouth dissolving strip in the field of drug delivery system.

KEYWORDS: Mouth dissolving strip, Ingredients, Formulation and Evaluation of strip.

INTRODUCTION

Mouth Dissolving Strip is a new technology developed for oral administration of active ingredients, together with the active ingredients it contains numerous excipients such as polymers and other additives like plasticizers, flavors, colors, sweeteners, surfactants,

thickening agents, disintegrants. The mouth dissolving strip is often used for delivering a drug systemically to attained the therapeutic or pharmacological effect. Mouth dissolving strip formulations have improved systemic bioavailability because it avoids first pass metabolism. When mouth dissolving strip are placed on the tongue, they quickly disintegrate with secretion, and the requirement of water is not needed. Therefore, they completely have an effect on the bioavailability of the drug, and thus the specified effect starts quicker. The oral mucous membrane is abundant in blood supply and more permeable. The mucous membrane of the mouth is a potential site for an immediate, sustained, and controlled drug delivery system. Available research models suggest that instead of disintegrants we can also use insoluble particles ex: Micro Crystalline Cellulose (MCC), Silica as a disintegration enhancer. To overcome difficulties related to swallowing of the solid unit dosage form (tablet & capsule), Oral film technology was invented. In the marketplace, the introduction of Mouth dissolving strip was strongly linked with the guidance of patients regarding the suitable administration by giving instructions like ‘‘do not chew/do not swallow’’. A typical Oral Dissolving Film (ODF) is usually equal to the size of a postage stamp.

MOUTH DISSOLVING STRIP

SPECIAL FEATURES OF FAST DISSOLVING ORAL FILM

- Thin elegant film
- Available in various size and shape
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration and rapid release
- Larger the surface area greater the bio-availability

IDEAL CHARACTERISTICS OF A SUITABLE DRUG CANDIDATE

- The drug to be incorporated should have low dose upto 40 mg.
- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially ionized at the PH of oral cavity.
- The drug should have pleasant taste.
- It should have the ability to permeate oral mucosal tissue.

LIMITATIONS OF MOUTH DISSOLVING STRIP

- Due to the narrow surface area of the buccal cavity, only little doses of drug can be delivered.
- Stability issues such brittleness and moisture absorption during storage.
- It is impossible to deliver medications that are unstable at buccal pH.
- The administration of drugs that irritate the mucosa is prohibited.

ADVANTAGES OF MOUTH DISSOLVING STRIP

- For pediatric, elderly, and psychiatric patients who have trouble swallowing tablets and other solid dosage forms, it is simple to administer.
- The film administered sublingually and buccally deliver the drug with high potential to improve the onset of action, lower the dose, and enhance the efficacy and safety profile of the medicament.
- All single unit dosage forms, soft gels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first pass effects.
- As a result, such formulations often require higher doses and generally have a delayed onset of action, which can be overcome using current oral film drug delivery systems that avoid these issues and yield quicker onset of action at lower doses.
- Mouth dissolving strip is more stable, durable and quicker dissolving than other conventional dosage forms.
- Mouth dissolving strip enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain precise amount of drug.
- Mouth dissolving strip ensures more accurate administration of drugs.

- Mouth dissolving strip can improves compliance due to the intuitive nature of dosage form and its inherent ease of administration.
- These properties are especially beneficial for pediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult.
- Mouth dissolving strip has ability to dissolve rapidly without the need for water provides an alternative to patients with dysphasia and to patients suffering from nausea, such as those patients receiving chemotherapy.
- Oral film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not to be possible in tablet or liquid formulations.
- From a commercial perspective oral film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition.

DISADVANTAGES OF MOUTH DISSOLVING STRIP

- Mouth dissolving strips have limitations in terms of the higher amount of drug that can be incorporated, the drug dose must be less than or equal to 30 mg for soluble drugs.
- Also, due to the nature of fast dissolving oral films, special packaging is needed.
- Dose uniformity is a challenge.
- It takes moisture from atmosphere.
- It requires special packaging for product's stability and safety.

TYPES OF ORAL FILMS

There are three different types of oral films:

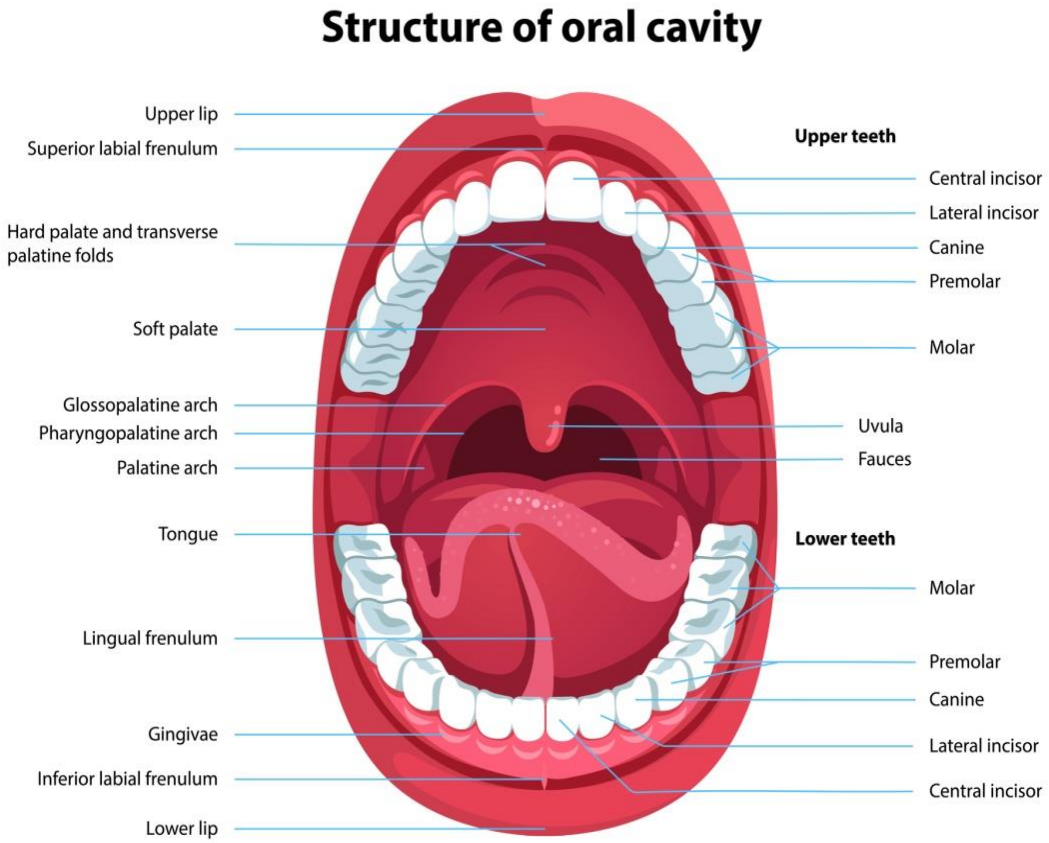
- Flash release wafers.
- Mucoadhesive melt away wafers.
- Mucoadhesive sustained release wafers

Comparison Between Orally Dissolving Films and Oral Disintegrating Tablet

S.NO	ORAL DISSOLVING FILM	ORAL DISSOLVING TABLET
1	Larger surface area gives greater dissolution	Less surface area gives less dissolution than oral dissolving film
2	These are flexible and durable	These are brittle and less durable than oral dissolving film
3	Only low dose can be incorporated	High dose can be incorporated.
4	Thickness are 50 to 500 μm.	Thickness as like convention tablet.
5	Patient compliance is less	Patient compliance is more

OVERVIEW OF THE ORAL CAVITY

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The oral mucosa in general is intermediate between that of the epidermis and intestinal mucosa in terms of permeability. It is estimated that the permeability of 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 because of the diverse structures and functions of the different oral mucosa.



SUBLINGUAL GLAND

Salivary glands are present in the floor of the mouth underneath the tongue. Sublingual glands are also known as the salivary glands that are located beneath the tongue secrete saliva which gets mixed with the food, so that the food gets lubricated, formed into a soft bolus and can be easily swallowed. Absorption of drugs is directly from the site into systemic circulation owing to its relatively lesser thickness, high permeability and rich blood supply they are also known as sublingual glands. They produce mucin in turn produces saliva. The

oral cavity is lined with mucous membrane which comprises of squamous cells and mucous glands. Salivary gland contains the group of cells which secrete saliva into the mouth through salivary ducts. Salivary gland includes comprises of Parotid, Submandibular and Submaxillary glands. The fluid which is produced by the glands gets mix with the food, so the food gets easily chewed. 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 follows in this way Sublingual > Buccal > Gingival >Palatal. Due to high permeability and rich blood supply, the sublingual route can produce rapid onset of action so the drug with short delivery period can be delivered and dose regimen is frequent.

MECHANISM OF ABSORPTION

Sublingual administration 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 are then drained into the systemic circulation. Upon sublingual administration drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. 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.

FACTORS AFFECTING ABSORPTION

- Solubility in salivary secretion: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption.
- Binding to the oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.
- PH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.
- Lipophilicity of the drug.
- For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.

- Thickness of the oral epithelium: As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

STANDARD INGREDIENTS OF MOUTH DISSOLVING STRIP

Following general composition of drug and excipients in percentage

1) Drug (1-30%)
2) Film forming polymer (40-50%)
3) Plasticizer (0-20%)
4) Salivary stimulant (2-6%)
5) Sweetening agent (3-6%)
6) Surfactant (Q.S)
7) Flavoring agent (Q.S)
8) Colouring agent (Q.S)

1) **Drug (1-30%)** The drugs selected oral films should possess good stability in saliva and water with low dose. 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 films. Any class of pharmaceutically active drugs that can be delivered orally such as expectorants, antianginals, antitussives, antihistaminic, antiepileptic, antianalgesic and antiulcer drugs.

Ideal drug candidate for drug delivery

- Drug should less than or equal to 30 mg.
- Low molecular weight drugs are preferable.
- It should have a pleasant flavor.
- It should be reasonably stable in both saliva and water.
- It need to be capable of penetrating the mucosal tissue of oral cavity.

2) **Film forming polymer (40-50%)** Water-soluble polymers are employed as film formers because they give the films a quick disintegration, a pleasant mouth feel, and mechanical qualities. Polymers can be employed individually or in mixture with others to create films with the necessary hydrophilicity, flexibility, mouth feel, and solubility. The rate of polymer disintegration reduces as the molecular weight of polymer film bases increases.

Ideal properties of polymer

- Polymers that are plain, nontoxic, and inexpressive should be used.
- It should have no flavor. It should be free of drainable toxins.
- It should be affordable and simple to obtain.
- It shouldn't be a major hindrance during the deterioration interaction.
- It must possess exceptional wetting and spreading qualities.
- It must be sufficiently flexible, shear, and able to strip.
- It should not induce additional oral disease and have a long time frame of realistic usability.

3) **Plasticizer (0-20%)** It serves as a key component in oral thin films. The plasticizers aid in enhancing the mechanical characteristics of the film, such as its tensile strength and elongation. Additionally, it makes the film less brittle. It might increase the strength and flow of polymer. The choice of plasticizers must be made carefully. It should interact well with the polymers, the drug, and the other excipients. The wrong selection could result in the film peeling, splitting, and cracking. Dimethyl, dibutyl, diethyl phthalate, tributyl, triethyl, actyl citrate, triacetin, propylene glycol, polyethylene glycol, and glycerol are some examples of plasticizers that are frequently employed.
4) **Saliva stimulating agent (2-6%)** Saliva stimulating drugs are used to boost saliva production in to accelerate the breakdown and dissolution of the oral film insight the mouth. It has a range of 2-6% that can be used alone or in mixture. Citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid are often used saliva-stimulating substances. Citric acid is the most popular of them.
5) **Sweetening agent (3-6%)** Sweeteners are typically used to cover up the bitter taste of some drugs. One can use natural and artificial sweeteners alone or together. Types of sweetener includes natural sweeteners, such as corn syrup solids, xylose, ribose, glucose, mannose, galactose, fructose, dextrose, and sucrose and artificial sweeteners aspartame, cyclamate, and saccharin. Acesulfame K, sucralose, alitame, and neotame.
6) **Surfactant (Q.S)** As a solubilizing, wetting, or dispersion agent, surfactants are employed. Surfactant is used to breakdown the film quickly and release the active ingredient. Surfactant can increase the solubility of poorly soluble drugs in rapidly dissolving oral films. Polaxamer 407, sodium lauryl sulphate, benzalkonium chloride, benzthonium chloride, tweens, and spans are a few examples.

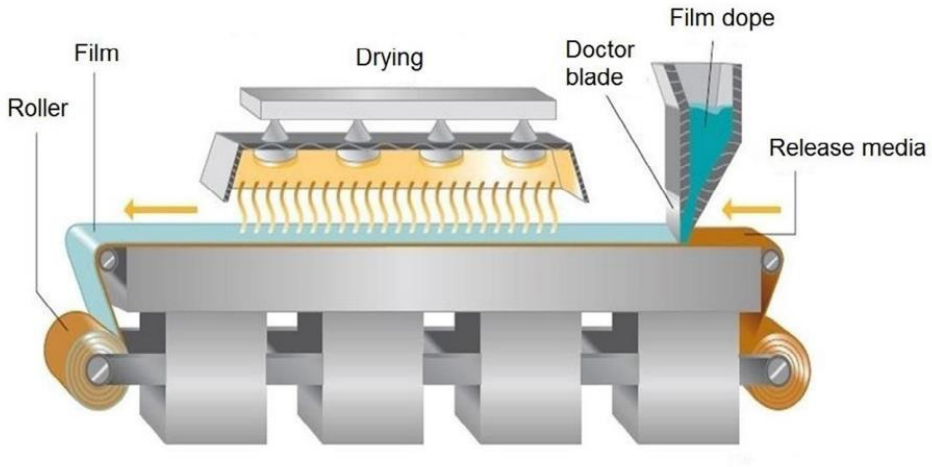
7) **Flavoring agent (Q.S)** Both natural and artificial flavors, including methyl salicylate, eucalyptol, thymol, artificial vanilla, cinnamon, various fruit flavors, mints like peppermint and menthol, and essential oils, may be used singly or in combination.
8) **Coloring agent (Q.S)** When some of the ingredients or drugs in the formulation are present in insoluble or suspension form, titanium dioxide or FD&C approved coloring additives are added (not exceeding concentration levels of 1%w/w).

METHOD OF PREPARATION OF MOUTH DISSOLVING FILM

The methods for manufacturing oral thin films include

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

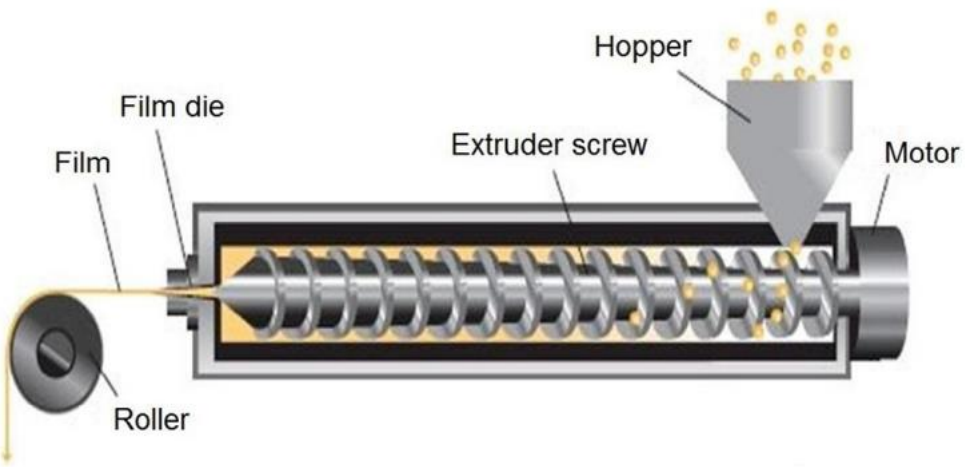
1) **Solvent casting method:** Polymers that are water soluble are dissolved to create a homogeneous solution. Drugs and other water-soluble ingredients are given a little amount of water to dissolve in. Continuous stirring is used to combine the two solutions. Applying a vacuum removes air bubbles that have become entrapped. The produced solution is cast onto Petri dish and then divided into bits.



2) **Semisolid casting method:** When acid-insoluble polymers are required for the film preparation, this approach is preferred. Gel mass is cast in to the films or ribbons using the semisolid casting technique, which uses heat-controlled drums. Gel mass is created by mixing a film-forming solution with an acid-insoluble polymer solution in sodium hydroxide or ammonium hydroxide. The polymers cellulose acetate phthalate and

cellulose acetate butyrate are insoluble in acids. The proportion of 1:4 acidinsoluble polymer to film-forming polymer should be taken.

3) **Hot-melt extrusion method:** In the hot melt extrusion procedure, the drug and carriers are first combined in solid form. After that, dry granular material is poured to the extruder. Processing of the granules inside the extruder barrel for about 3–4 minutes, the speed of screw is set at 15 rpm. The recommended processing temperatures are 650C, 800C, 1150C, and 1000C for zones one through three (zone-4). The extrudate was subsequently compressed insight cylindrical calendar to produce a film.



4) **Solid dispersion method:** In this approach, more than one drug candidate are dispersed in an non reactive carrier in a conventional dosage form while amorphous hydrophilic polymers are present. To create a solution, Active pharmaceutical ingredient is dissolved in a appropriate solvent. A solution is incorporated to the melt of an appropriate polymer (PEG) beneath 70° C without extracting the liquid solvent. Finally, solid dispersion is formed into films using dies.
5) **Rolling method:** The rolling approach involves preparing a drug solution or suspension with a film-forming polymer before putting it through the roller. Specific rheological considerations should be made for the suspension. The majority of the solvent is composed of water and an alcohol-water mixture. After the film has dried on the rollers, it is cut into the desired shapes and sizes.

EVALUATION OF MOUTH DISSOLVING STRIP OF DISLORATADINE

Thickness: A micrometer screw gauge may be used to precisely measure it at several predetermined points. This is crucial for ensuring consistent dosing in the strip by measuring

film thickness uniformly. A micrometer was used to determine film thickness. Each sample was measured three times to get an average thickness. Air bubbled, nicked, or torn samples, as well as those with mean thickness variations over 5%, were not included in the study.

Folding Endurance: The precise value of folding endurance is determined by counting the Number of times the film may be folded at the same area before breaking. The prepared films were physically tested for their folding durability. A square of film (2x2 cm^2) was cut precisely and then folded over and over again until it snapped.

Physical Appearance/Texture: The film's physical characteristics were evaluated by looking at it and touching it with two fingers.

Determination of Weight Variation: The films were measured and sliced into (2x2 cm^2) Electronic balance was used to figure out the difference in weight.

In-vitro Disintegration Studies: The film's disintegration and dissolution properties might be inferred from its disintegration time. The film used in this experiment measured exactly (2x2 cm^2) and was put in a beaker containing 10 milliliters of artificial saliva. The in-vitro disintegration time was recorded as the amount of time the film took to shatter.

Measurement of Tensile Strength

Two-by-two centimeter strips of film were produced. Each strip was put in the tensile grips of the testing machine in a longitudinal orientation. The strips were dragged by the top clamp at a speed of 60 mm/min across the head, with an initial grip separation of 10 mm. After the credits rolled, test was judged complete. Each film's measurements were taken three times. The film's quality was determined by calculating three mechanical properties: tensile strength, elastic modulus, and percent elongation. The tensile strength of a material may be determined by applying a load until the film specimen ruptures; this is done by taking the average of three measurements and using the following equation to describe the cross sectional area of the broken film.

$$\textbf{Tensile Strength} = \frac{Load at failure}{Strip thickness X Strip width} \textbf{ x 100}$$

Measurement of Percentage elongation: The following formula was used to calculate the elongation in percentage terms.

$$\text{Percentage Elongation} = \frac{Increase\ in\ length\ of\ strip}{Initial\ length\ of\ strip} \text{x } 100$$

Determination of Drug Content: Drug concentration was calculated by dissolving sheets of known area (2x2 cm^2) in a suitable solution. By using a UV- spectrophotometer was used to quantify the concentration of drug in the sample. Standard calibration curv was used to calculate the drug concentration.

In-vitro Dissolution Studies

The paddle or basket apparatus mentioned in the pharmacopoeias used to conduct dissolution testing. The sink conditions and API dose will primarily be taken into consideration while choosing the dissolving medium. The tendency of the strip to float onto the dissolving media when the paddle equipment is used frequently makes the dissolution test.

Surface pH: The potential for adverse consequences in vivo was studied by measuring the surface pH of rapidly dissolving films. The oral mucosa may be irritated by a surface pH that is too acidic or alkaline; hence it was decided to maintain a pH value as near to neutral as feasible. After soaking the films in distilled water for 30 minutes at room temperature, they were placed in a closed Petri dish. The pH of the solution at the surface was measured using a digital pH meter.

Research on Stability According to the ICH recommendation: The oral films were stable for 3 months when kept at 40 degrees Celsius and 75% humidity. The film's morphological features, disintegration time, drug content, and in vitro dissolution studies should be monitored during storage.

CONCLUSION

The present review reveals that Mouth dissolving strip are novel approaches in the field of the pharmaceutical industry. There are various approaches for the preparation of mouth dissolving strip. The major concept behind the formulation of mouth dissolving film was to deal with the issue of swallowing typical oral dose forms among medical specialty, geriatric, and psychiatric patients with dysphasia or for patient those who have difficulty in swallowing. The formulation delivers the drug directly into systemic circulation hence bioavailability gets improved and minimizes adverse effects with higher safety. Mouth dissolving films are promising dosage form as they have more patient compliance and rapid

onset of action. Moreover they are potential candidate for oral route as they can deliver drug locally as well as systematically. Due to these advantages mouth dissolving strip used to treat patient efficiently.

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