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ORALLY FAST DISSOLVING STRIPS: A NEW APPROACH TO ORAL DRUG DELIVERY SYSTEM

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ABSTRACT
Mouth Dissolving Films (MDFs) are an innovative and emerging drug delivery system designed to dissolve quickly upon contact with saliva, offering ease of administration and improved patient compliance. These thin, flexible strips are particularly beneficial for pediatric, geriatric, and dysphagic patients who face difficulties swallowing conventional tablets or capsules. MDFs deliver drugs through oral mucosal absorption or gastrointestinal pathways, ensuring rapid onset of action. The formulation of MDFs typically involves hydrophilic polymers like hydroxypropyl methylcellulose, polyethylene glycol, or polyvinyl alcohol, which provide the necessary mechanical strength and dissolvability. The films are prepared using techniques such as solvent casting, hot-melt extrusion, or rolling methods. The incorporation of active pharmaceutical ingredients, plasticizers, sweeteners, and flavoring agents is crucial for achieving desired drug release profiles, film stability, and patient acceptability. Key advantages of MDFs include precise dosing, portability, and avoidance of first-pass metabolism, making them ideal for both systemic and local drug delivery. However, challenges like limited drug loading capacity, taste masking, and ensuring film uniformity and mechanical integrity require optimization during formulation development. This review highlights the critical aspects of MDFs, including their formulation, manufacturing techniques, evaluation parameters, and applications. Recent advancements, such as the use of nanotechnology and bio-adhesive polymers, have expanded the scope of MDFs for delivering a wide range of therapeutic agents. As a patient-friendly alternative, MDFs hold great promise for improving medication adherence and therapeutic outcomes. Further research is warranted to overcome existing limitations and explore novel applications.

KEYWORDS: Nanotechnology, Mouth dissolving film, Taste masking, Bio-Adhesive Polymer.

1. INTRODUCTION[1]
As an alternative to fast-dissolving tablets, fast-dissolving films have garnered attention recently. The films can be consumed without the need for extra liquid because they are made to disintegrate in a matter of seconds when they come into touch with a wet surface, like the tongue. This ease of use boosts patient compliance and gives a commercial edge. Since the medication enters the bloodstream directly, first pass effects and gastrointestinal tract degradation are prevented. Because of these features, this formulation is most well-liked and acceptable by older and pediatric patients as well as those who are afraid of choking.[1]

In US markets, over-the-counter pain relievers and motion sickness films are marketed. Transdermal drug delivery technology is being used by numerous businesses to create thin film formats. Recent developments pertaining to the formulation of fast-dissolving buccal films and their assessment criteria are compiled in this review. Initially developed in the late 1970s, fast-dissolving drug delivery devices helped elderly and juvenile patients who had trouble swallowing tablets and capsules. Buccal drug delivery has grown in importance as a drug administration method recently. Adhesive tablets, gels, ointments, patches, and, more recently, the use of polymeric films for buccal delivery—also referred to as mouth dissolving films—are among the bioadhesive mucosal dosage forms that have been created. The stratified squamous epithelium that covers the buccal cavity's surface is essentially separated from the lamina propria and submucosa, the underlying tissue, by an undulating basement membrane.[2] It's interesting to note that the buccal mucosa has permeability that is around 4-4,000 times higher than the skin's, but lower than the intestine's.[3]

Therefore, molecules with little skin penetration can be absorbed very well through buccal administration. The principal otiral mucosa permeability barrier arises from intercellular material that is sourced from the so- called "membrane coating granules" that are located at the topmost 200 µm layer.[4]

Depending on the active medicinal ingredient, these dosage forms have a shelf life of two to three years, however they are quite susceptible to moisture in the environment.[5] The following characteristics of an optimal fast-dissolving delivery mechanism should be present:High stability, mobility, simplicity in handling and administering, lack of need for additional processing or packaging materials, taste that is pleasing, and no special packaging material is required.[1]

A series of flat films termed oral films—also referred to as oral wafers in related literature—are inserted into the oral cavity. The third type, oral film systems, has been around for a while, but in terms of fast-dissolve pharmaceutical drug delivery, they are currently of particular interest. In recent years, dissolveable OTF, also known as OS, has transformed from breath strips used in the confection and oral care industries to a unique and extensively embraced form by consumers for the delivery of vitamins and personal care items. Businesses that had previously developed polymer coatings with active pharmaceutical ingredients (APIs) for transdermal medication delivery seized the chance to transfer this expertise to OTF forms. OTFs are now in the early to mid-development stages for prescription pharmaceuticals and are a tried-and-true method for systemic administration of APIs for over-the-counter (OTC) treatments.[2]

Nonetheless, various dosage forms are being offered for therapeutic purposes in the pharmaceutical markets of the United States and Europe. The first oral strips (OS) were created for mouth freshening purposes and were dubbed Listerine® pocket packsTM by the large pharmaceutical corporation Pfizer. The first therapeutic oral thin films (OTF) to treat sore throats were Chloraseptic® comfort strips, which included seven benzocaine.

1.1 Anatomy and physiology of oral cavity

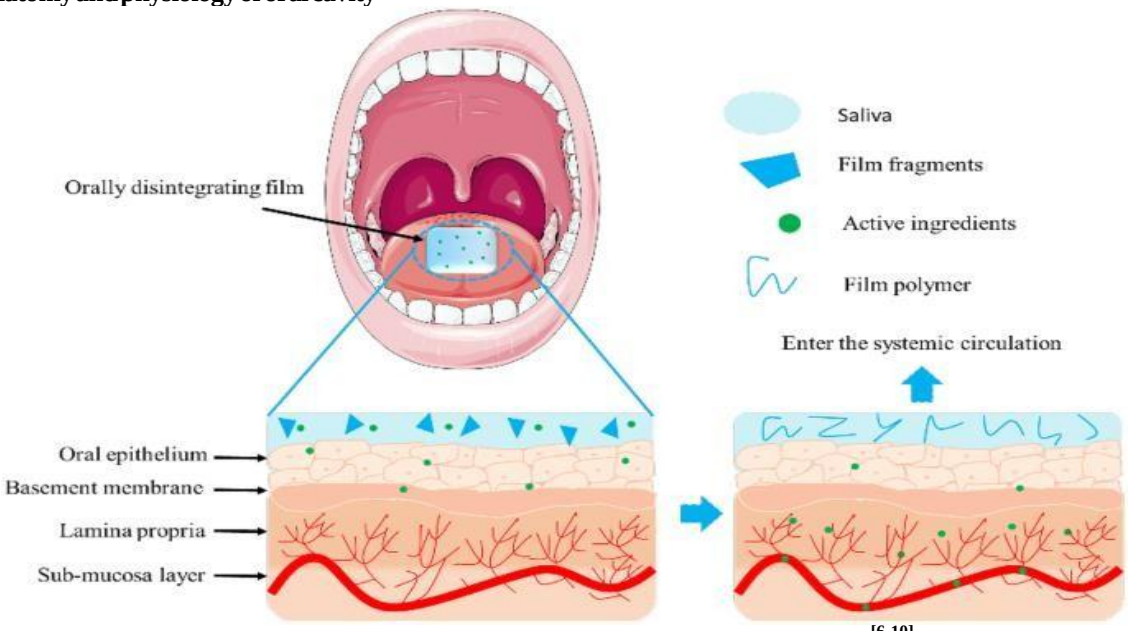

Fig. 1: Anatomy and physiology of oral cavity Oral cavity.[6-10]

The mucus produced by the 40–50 cell layer of the oral tissue epithelium is composed of proteins and carbohydrates. The mucosal thickness varies between 100 and 200 µm at the base of the mouth, the tongue, and the gums. Mucus, a small gel-like fluid secreted by the submucosal layer, is composed of 90%–99% water, 1%–5% water- insoluble glycoprotein, and other components like proteins, enzymes, electrolytes, and nucleic acids. In contrast, saliva and parotid are secreted by lobules within the salivary glands from the salivary duct in the vicinity of the sublingual canals and submandibular teeth. Most frequently, small salivary glands are located on the mucosa of the cheeks and lips. About 1-2 ml of saliva is secreted in total in a minute.

The mucus, water, the enzymes lysozyme and amylase, mineral salts, immunoglobulins, and blood clotting factors make up saliva. Saliva and mucin function as barriers for the oral mucosa as well. There are two distinct regions in the mucosal epithelial structure: the lipophilic space between cells and the lipophilic membrane of the stratified epithelium and the more hydrophilic region. In terms of substance permeability, the oral mucosa can withstand conditions that the intestinal mucosa and the epidermis cannot. The buccal mucosa is thought to have 4–4000 times greater

permeability than the skin. There are two primary drug absorption pathways provided by the mucosal epithelium: the transcellular (intercellular) and paracellular (intercellular) pathways (fig.). While more hydrophilic molecules can enter the intercellular space due to their polarity, particles with a high partition coefficient can more easily pass through the lipophilic structure that makes up cell membranes. The drug's absorption depends on whether it is hydrophilic, hydrophobic, or amphiphilic Oral Thin Film Market was valued at USD 3.92 Bn in 2023, and it is expected to reach USD 8.51 Bn by 2030, exhibiting a CAGR of 11.71% during the forecast period 2024- 2030.

1.2 Global Oral Thin Film Market Overview[11-12]

Oral thin films refer to a drug delivery dosage device constituted of a mono polymeric thin film deposited in the mouth for a fast release of an active pharmaceutical ingredient (API) when put on the tongue. Oral thin film (OTF) is used to deliver medicinal chemicals into the mouth or stomach, where they are absorbed and transferred directly to the circulatory system.

The report explores the Global Laboratory developed test Market's segments (Product, Indication, Distribution Channel). Data has been provided by market participants, and regions (North America, Asia Pacific, Europe, Middle East & Africa, and South America). The MMR market report provides a thorough analysis of the rapid advances that are currently taking place across all industry sectors. Facts and figures, illustrations, and presentations are used to provide key data analysis for the historical period from 2018 to 2023. The report investigates the Global Oral Thin Film Market's drivers, limitations, prospects, and barriers. This MMR report includes investor recommendations based on a thorough examination of the Global Oral Thin Film Market's contemporary competitive scenario.

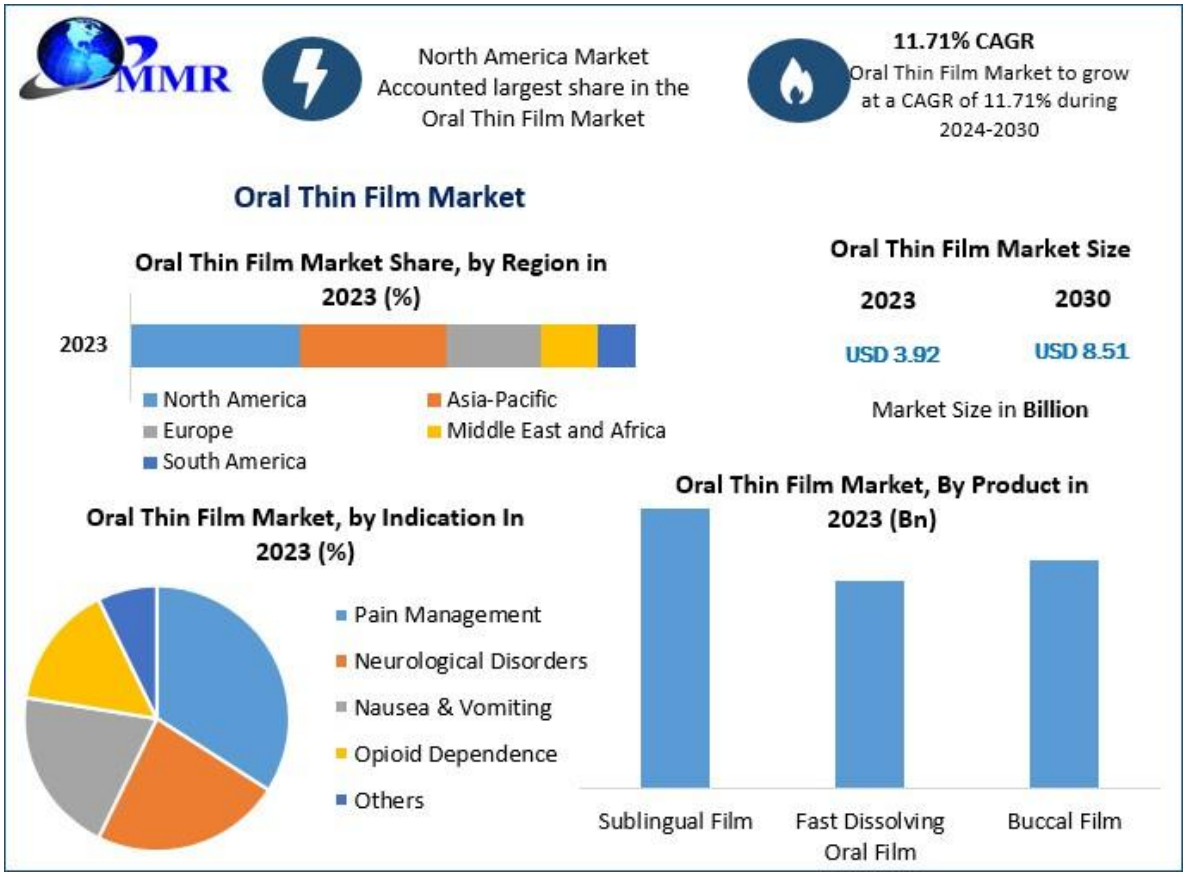

Fig. 2: Global Oral Thin Film Market Overview.

Oral Thin Film Market Regional Insights

North American Market valued highest market share in 2023.

During the forecast period, North America is expected to hold the largest share of the worldwide oral thin films market. The region's market is being driven by higher penetration of oral thin films, product availability, and the presence of a large number of providers compared to other areas.

The demand for oral thin films has been continuously increasing in the United States, mostly for the treatment of opioid addiction, amyotrophic lateral sclerosis (ALS), and schizophrenia, among other illnesses. Many more are in the works to treat chronic illnesses like migraine and Alzheimer's disease.

Due to the presence of local as well as global companies and an increase in demand for oral thin films in the region, the market in Asia Pacific is likely to grow at in

forthcoming. In the foreseeable future, the oral thin film market in Europe is expected to grow rapidly. During the forecast period, Japan and China are expected to be lucrative markets for oral thin films. The presence of a high senior patient population with dysphagia, as well as an increase in healthcare expenditure in these nations, are expected to move the Asia Pacific market forward in the coming years.

The objective of the report is to present a comprehensive analysis of the Global Oral Thin Film Market to the stakeholders in the industry. The past and current status of the industry with the forecasted market size and trends are presented in the report with the analysis of complicated data in simple language. The report covers all the aspects of the industry with a dedicated study of key players that include market leaders, followers, and new entrants.

PORTER, PESTEL analysis with the potential impact of micro-economic factors of the market have been presented in the report. External as well as internal factors that are supposed to affect the business positively or negatively have been analyzed, which will give a clear futuristic view of the industry to the decision-makers.

The reports also help in understanding the Global Oral Thin Film Market dynamic, structure by analyzing the market segments and projecting the Global Oral Thin Film Market size. Clear representation of competitive analysis of key players by Vehicle type, price, financial position, product portfolio, growth strategies, and regional presence in the Global Oral Thin Film Market make the report investor's guide.

Growth Factors

- Increasing demand for oral thin films from the pharmaceutical and nutraceutical industries as a result of their benefits such as ease of use, accurate dosage, and improved patient compliance.
- Growing research and development activities for the development of novel oral thin film drug delivery systems that can improve therapeutic outcomes.
- Rising number of product approvals by regulatory agencies for various oral thin film products in different geographies. This is likely to boost the market growth in the coming years.
- Proliferation of contract manufacturing organizations (CMOs) that offer comprehensive services for developing oral thin films is projected to drive market growth over the forecast period, etc.

1.3 Literture survey

Name of author	Year of study	Abstract
Ruchita Badekar	Feb 2024	One of the most creative and patient-focused novel drug delivery systems is Orodispersible Thin Films (OTF). Numerous pharmaceutical companies and academic experts worldwide are currently investigating the potential of these films for delivering drugs derived from both synthetic and natural sources. The beauty of this special drug delivery method is that, as we can see from the subjects' consumption of conventional dosage forms (tablets, capsules), they don't require water to be consumed. Furthermore, these delivery methods do a great job of encouraging patient compliance in general, especially in the case of both older and pediatric patients. This review shows a detailed review of oral thin film its applications and method of preparation; mainly focus of this research is thin film introduction to researchers and last 10 y of research on thin film with drugs and polymers used in research.
P. Toniya Naga Purna Priyanka	March- 2024	The pharmaceutical companies are looking for novel ways to distribute drugs, and one such way is through oral films. It has been said that oral films offer an alternative to traditional dose forms. They offer rapid, local, or systemic effects and are a very flexible platform. Furthermore, patients with dysphagia, elderly, pediatric, or bedridden patients, as well as those who have difficulty accessing water, can simply utilize these devices on their own. There are several ways to administer this drug delivery system, including transdermally, ocularly, buccally, sublingually, and orally. These review looks at oral dissolving films from a modern perspective and provides insight into the industry's expanding global market share as a result of expanding research areas and technological advancements. Simultaneously, it offers a summary of the crucial elements linked to formulation design that impact oral film technology, such as oral film design, physiological and auatomical constraints, appropriate manufacturing process selection, characterization methods, and the physicochemical characteristics of drugs and polymers. It also offers information on the most recent oral film products that different pharmaceutical companies have developed.
Quazi bilal, shrikrushna subhash unhal	March 2020	Fast Dissolving Drug Delivery systems have developed various fast disintegrating preparations like mouth dissolving film, MDT. Oral thin film are new dosage form that are

		prepared from hydrophilic polymer which are when placed in mouth, buccal cavity disintegrate rapidly. Mouth dissolving film is superior as compare to mouth dissolving tablet as the cost of production is low. Geriatric and pediatric patients are facing difficulty in swallowing of tablet and capsule, the oral film can bypass it, along with that it has other advantages like self-administrable, fast dissolving, rapid absorption that make it versatile dosage form. The aim of present study is to enlighten specifically different polymer along with their concentrations and applications. This study also focuses on use of plasticizer, polymer, sweetener, different methods which are used for the preparation of oral films and various evaluation parameter of the film.
Satankar Rahul, dr. Agrawal shikha	August 2019	The aim of present investigation was to formulate the oral films of Nitroglycerine belongs to a class of drugs known as nitrates. Angina occurs when the heart muscle is not getting enough blood. This drug works by relaxing and widening blood vessels so blood can flow more easily to the heart. Oral films were prepared by solvent casting method using film forming polymers and propylene glycol, PEG 400 as plasticizers and evaluated for mechanical properties, disintegration and in vitro dissolution.All formulations showed good mechanical properties. Keywords: - Oral film, Nitroglycerine, Plasticizer, polymer, Solvent casting method
Vaishali inodhe	2012 mar-apr	Hypertension is a major cause of concern not just in the elderly but also in the youngsters. An effort was made to formulate a fast dissolving film containing telmisartan which is used in the treatment of hypertension with a view to improve the onset of action, therapeutic efficacy, patient compliance and convenience. The major challenge in formulation of oral films of telmisatran is that it shows very less solubility in the pH range of 3-9. Various film forming agents and polyhydric alcohols were evaluated for optimizing composition of fast dissolving films. Fast dissolving films using hydroxypropyl methylcellulose,

1.4. CLASSIFICATION OF FAST DISSOLVING TECHNOLOGY[6]

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

1.4.1 Lyophilized systems.
1.4.2 Compressed tablet-based systems.
1.4.3 OTF.

1.4.1 Lyophilized System

The technology underlying these systems forms tablet-shaped units by combining a medication suspension or solution with additional structural excipients and using a mold or blister pack. After that, the tablets or units are frozen and lyophilized inside the mold or pack. Because of the extremely high porosity of the resultant units, some tablet-based systems can dissolve and absorb water or saliva very quickly. Compared to tablet-based systems, the units dissolve more quickly and can incorporate a variety of taste-masked components.

1.4.2. Compressed tablet-based systems

The production of this system involves the direct compression of excipients utilizing ordinary tablet technology. The hardness and friability of tablet technology vary depending on the manufacturing process. This leads to different packaging requirements and disintegration performance, as demonstrated by CIMA Labs and PackSolv. When creating fast dissolving tablets, water soluble excipients, superdisintegrate, or effervescent components are used to enable quick water penetration into the tablet core, resulting in a faster rate of disintegration than conventional tablets. They may dissolve more slowly than thin-film or lyophilized dose forms, which could be a drawback. A growing number of technological enterprises, branded businesses, and generic pharmaceutical companies are using the loose compression tablet technique.

1.4.3 OTF

A collection of flat films termed oral films—also referred to as oral wafers in related literature—are inserted into the oral cavity. Meltable Over the past few years, OTF or OS—also known as breath strips—have developed from the confection and oral care businesses into a unique and broadly accepted method of delivering vitamins and personal care goods to customers. OTFs are a tried-and-true technique used today to deliver APIs systemically to over-the-counter (OTC) drugs.

02. CLASSIFICATION OF OTF[7]

There are three subtypes of oral fast dissolving films;

2.1. Flash release.
2.2. Mucoadhesive melt-away wafer.
2.3. Mucoadhesive sustained release wafers.

Table No. 1: Classification of OTF.

Properties	Flash release	Mucoadhesive melt-away wafers	Mucoadhesive sustained released wafers
Area(cm^2)	2-8	2-7	2-4
Thickness	20-70	50-500	50-250
Structure	Single layer	Single or multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low/insoluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspension and/or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival,(other region in the oral cavity)
Dissolution	60s	In few minutes forming gel	Maximum 8-10h
Site of action	Systemic or local	Systemic or local	Systemic or local

2 SPECIAL FEATURES OF FAST DISSOLVING FILMS[8]

- A film need to be attractive and slender.
- Comes in a range of forms and sizes.
- Inconspicuous.
- It ought to fit into the mouth cavity with ease.
- Needs to break down quickly without water.
- Quick release
- Easy administration for patients with mental illness, disability, and lack of cooperation.
- No water needed.
- Quick disintegration and dissolution of the dosage form.
- No risk of choking.
- High drug loading and ability to provide liquid medication advantages in the form of solid preparation.
- Cost-effectiveness and excellent mucoadhesion.
- Fast-dissolving films can be formulated in a variety of shapes and sizes

3 ADVANTAGES[9]

- Dosing convenience.
- Water is not required.
- There isn't a choke risk.
- Masking taste.
- Increased steadines.
- The medication has a diminished hepatic first pass effect when it enters the bloodstream.
- Local and site-specific activities.
- Accurate dosage compared to syrup.
- Possessing a wide surface area that facilitates quick disintegration and dissolving within the oral cavity.

4 DISADVANTAGES OF OS

The drawback of not being able to incorporate high dose within the strip. It is recommended to use a dose of 1–30 mg.

- The thickness while casting the film is one of the many technical issues that still exist with the use of film strips. Casting cannot be done on glass Petri plates.
- Achieving dose consistency with these dosage forms presents another technological issue.
- Film packaging need for specialized tools, and it's challenging to pack Because of its hygroscopic nature, it needs to be stored in dry environments.
- It also demonstrates the effervescent, fragile granule property.
- To ensure the stability and safety of the items, they need appropriate

5 STANDARD COMPOSITION OF ORAL FAST DISSOLVING STRIP[10]

Oral dissolving film is a thin film with an area of 1-20 cm2 (depends on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30 mg. Formulation considerations (plasticizers, etc.) have been reported as important factors affecting mechanical properties of the films. Table 3 lists the standard composition of fast dissolving strip along with the various ingredients used in the formulation of fast dissolving strips.

6.1. API
6.2. Polymer
6.3. Plastisizer
6.4. Surfactant
6.5. Sweetening agents
6.6. Siliva stimulating agent
6.7. Fillers, colour, flavors

Table No. 2: Std. Composition Of OTF.

Ingredients	Amount	Exzample	Uses
Drug	5-30 %w/w	Antiallergic, antiemetic, antiepileptic, antimigrant	Therapeutic activity
Polymer	45%w/w	Hpmc E3, E5, E15, k3,	Ability to forming film
		Methyl cellulose A3, A6, A15, pullulan, carboxymethylcellulose cekol30, polyvinyl koonpyrollidone pvp k90, pectin, gelatin, sodim, hydroxypropylcellulose, polyvinyl alkohol, matodextrin	
Plastisizer	0-20%w/w	Glycerol, dibutyl pthallate, polyethylene glycol,	Increase flexibility reduce bitterness of film

Surfactant	q. s.	Sodium lauryl sulphate, tween, span, benzalkonium alkinium cloride etc.	Solubilizing agent and wetting agent
Sweetening agents	3-6%w/w	Saccharin, cyclamate, aspartame	Enhance the palatability
Saliva stimulating agent	3-6%w/w	Citric acid, malic acid, lactic acid, ascorbic acid	Increase saliva stimulation
Fillers, colour, flavors	q. s	FD and C color, US FDA approved flavors	to mask odour of drug ,to give elegancy to film

6.1. Active Pharmaceuticals Agent

Any type of pharmaceutically active chemicals that can be delivered orally or through the buccal mucosa, respectively, may contain the active ingredient. The literature states that API can be added in the range of 5% to 25% w/w of the polymer's total weight. The medication dosage should be in milligrams (less than 20 mg/day) for the most effective formulation. The greatest candidates for quickly dissolving buccal films are medications that are strong, exhibit a high first pass metabolism, and have noncompliant patients. The creation of rapidly dissolving films has piqued the interest of researchers studying the following medical conditions: gastrointestinal disorders; pediatrics (antitussive, expectorant, antiasthamatics); geriatrics (antiepileptic, expectorants); pain (e.g., migraine); CNS (e.g. antiparkinsonism therapy).

Acrivastine, azatadine maleate, loratidine, phenylephrine hydrochloride, dextromethorphan hydrochloride, ketoprofen, sumatriptan succinate, zolmitriptan, loperamide, famotidine, nicotine, caffeine, diphenhydraminel hydrochloride, and pseudophedrine hydrochloride are a few of the preferred active agents. Their amounts per strip are well known in the industry.

6.1.1. Ideal characteristics for suitable drug candidate[11]

- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.

6.2. Polymers[12]

A range of polymers can be used to create buccal films that dissolve quickly. To achieve the required film qualities, the polymers can be utilized singly or in combination. The film that is obtained need to be sufficiently durable to prevent any damage while handling or transit. The kind and quantity of polymers used in the formulation determine how sturdy the strip is. The most popular polymers used to prepare fast dissolving films are xanthine gum, tragacanth gum, guar gum, acacia gum, methylmethacrylate co-polymer, hypromellose, pullulan, gelatin, hydroxypropylmethyl cellulose, hydroxyethylcellolose, hydroxypropylcellulose, polyvinylpyrrolidone, carboxymethylcellulose, polyvinylalchohal, sodium alginate, and xanthine gum. Using the solvent casting approach, several polymers, including pullalan, eudragit RL100, gelatin, PVP, PVA, HPMC E15, HPMC K4M, and HPMC E5, were combined to create quickly disintegrating buccal films. Pullalan is the ideal polymer for oral fast-dissolving strips, according to the results.

6.3. Plasticizers

An essential component of the formulation for the quickly dissolving buccal films is plasticizer.[13–14] The inclusion of plasticizer can enhance the mechanical properties of the films, such as their tensile strength and elongation. Additionally, it lessens the brittleness and increases the strip's flexibility. By lowering the polymer's glass transition temperature, they also enhance the strip's characteristics. The addition of plasticizer also improves the polymer's flow. These characteristics are impacted by variations in their concentration. The choice of plasticizer will be based on how well it works with the polymer and what kind of solvent was used to cast it. Triacetin, di- butylpthalate, glycerine, sorbitol, propylene glycol, polyethylene glycol, triethyl citrate, acetyl triethyl citrate, and other citrate esters are examples of plasticizers. The usual concentration of plasticizers is 0–20% w/w of the dry polymer weight.[15] When the plasticizer is used improperly, it might cause the film to split, peel, or crack. It can also slow down how quickly the medication absorbs.

6.4. Surfactants[16]

Surfactants are employed as dispersing, wetting, or solubilizing agents to disintegrate films quickly and release active ingredients right away. Additionally, surfactants increase the solubility of poorly soluble medications in quickly dissolving buccal film. Among the frequently utilized are tweens and spans, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, and polaxamer 407.

6.5. Sweeting Agents[17]

Sweeteners are now a crucial component of pharmaceutical preparations meant to dissolve or disintegrate in the mouth. Sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose are the traditional sources of sweeteners. Compared to sucrose and dextrose, fructose's sweetness is tasted more quickly in the mouth. Because fructose is sweeter than sorbitol and mannitol, it is a common sweetener. Since they also offer a pleasant mouthfeel and cooling effect, polyhydric alcohols like sorbitol, mannitol, and isomalt can be utilized in conjunction. One important consideration when creating oral preparations is the lack of bitter

aftertaste and reduced carcinogenicity of polyhydric alcohols. The use of artificial sweeteners in pharmacological formulations has grown in popularity. The first generation of artificial sweeteners includes aspartame, cyclamate, and saccharin. The second generation includes acesulfame K, sucralose, alitame, and neotame. More than 200 and 600 times as sweet are acesulfame K and sucralose, respectively. In comparison to sucrose, neotame and alitame have a sweetening capacity of over 2000 and 8000 times, respectively. The South American plant Stevia rebaudiana is the source of the herbal sweetener Rebiana, which has more than 200–300 times the sweetness of regular sugar.

6.6. Saliva Stimulating Agents

In order to facilitate the faster disintegration of the rapid dissolving strip formulations, saliva stimulating chemicals are used to boost the rate of saliva production. Salivary stimulants can generally be obtained from acids used in meal preparation. Among the few instances of salivary stimulants, citric acid is the most favored, followed by malic acid, lactic acid, ascorbic acid, and tartaric acid.[18]

6.7. Flavoring Agents[19]

Flavoring agents can be chosen from a variety of plant components, including leaves, fruits, and flowers, as well as synthetic flavor oils and oleo resins. You can use flavors singly or in combination. Any flavor can be added, including sour fruit flavors like lemon or orange, sweet confectionary flavors like vanillin or chocolate, or fruit essences like apple, raspberry, cherry, or pineapple. Other flavor options include intense mints like peppermint, sweetmint, spearmint, wintergreen, cinnamon, and clove. The type and strength of the flavor determine how much flavor is required to cover up the taste.

6.8. Coloring Agents

A wide variety of colors are offered, including bespoke pantone-matched hues, FD&C colors, EU colors, natural coloring agents, concentrated natural juices, and pigments like titanium oxide, silicon dioxide, and zinc dioxide. The concentration limits of 1% w/w should not be exceeded by any of these coloring agents. When some medications or chemicals in the formulation are present in an insoluble or suspension state, these agents are added.

7. Methods of manufacture of fast dissolving films

One (or a combination) of the following processes may be used to manufacture the oral films:

7.1. Solvent casting.
7.2. Hot-melt extrusion
7.3. Semisolid casting
7.4. Solid dispersion extrusion
7.5. Rolling.

7.1. Solvent Casting

The solvent casting method is the preferred method for formulating fast-dissolving buccal films. In this method, the drug and other excipients are dissolved in a suitable solvent after the water-soluble ingredients have been dissolved to form a clear, viscous solution. The two solutions are then combined, swirled, and dried in a Petri plate. To create a clear, viscous solution, water-soluble components are dissolved in H2O, while API and other agents are dissolved in an appropriate solvent. Both the solutions are mixed resulting solution is cast as a film and allowed to dry Film is gathered.

Hydroxypropylmethylcellulose, hydroxypropylcellulose, pullulan, sodium alginate, pectin, and carboxymethylcellulose are water-soluble hydrocolloids that are used to make films.

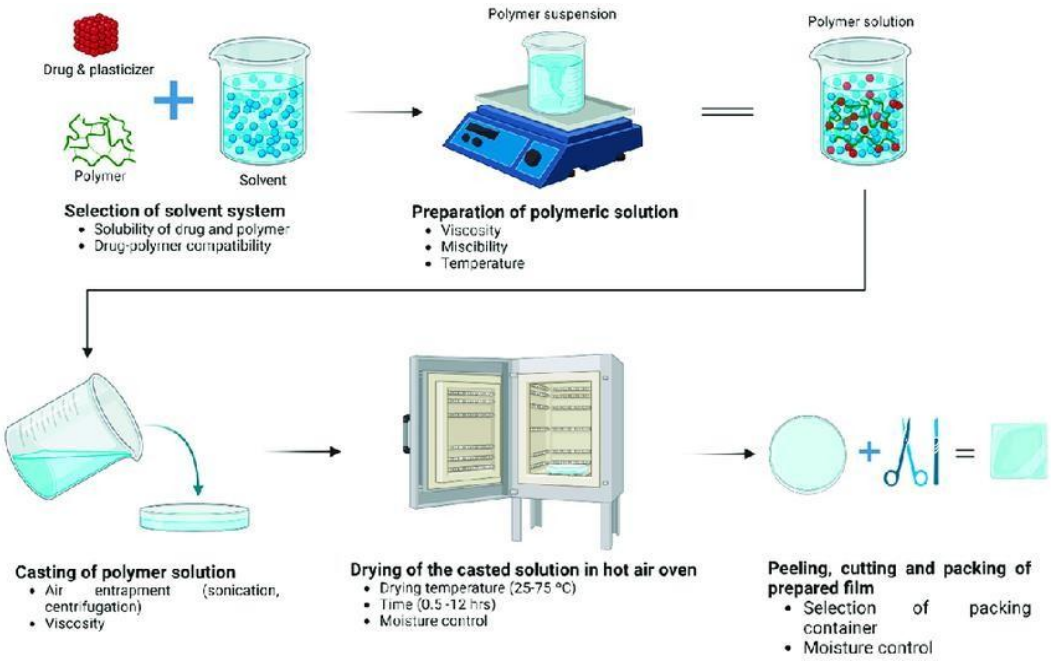

Fig. No. 3: Solvent Casting Method.

Table No. 3: Examples of fast dissolving films prepared by solvent casting method.

Sr. No.	Drug	Polymer	Plastisizer	Sweetening agent
1	Ondansetron	Polyvinylalcohal, polyvinyl pyrrolidone, Carboopol 934P	Propylene glycol or PEG 400	Mannitol or sodium saccharin
2	Maltodextrin	Polyvinyl alcohol	Glycerol	Glycerin
3	Salbutamol	HPMc	Glycerol	Aspartame

7.2. Hotmelt extrusion[20]

Granules, prolonged release tablets, and transdermal and transmucosal medication delivery systems are frequently made via hot metal extrusion. The pharmaceutical sector began using melt extrusion as a manufacturing tool in 1971. The medication is combined with solid carriers. The mixture is melted by an extruder with heating. Ultimately, the dies form the melt into films.

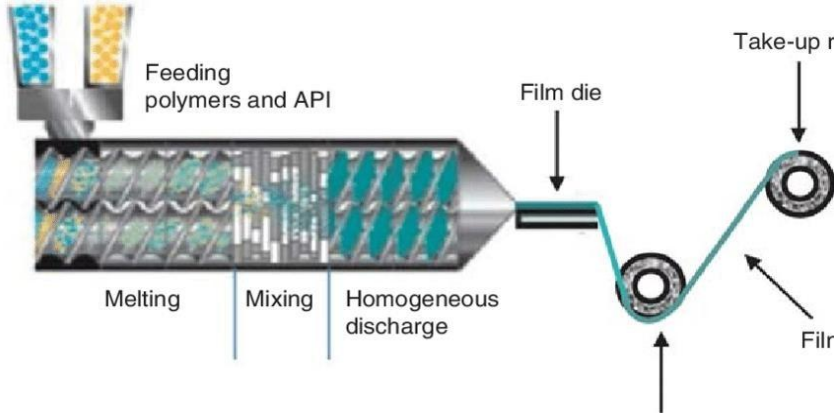

Fig. No. 4: Holtmelt Extrusion.

Hot melt extrusion has several benefits, such as reduced number of operation units, less product waste, potentialfor scaling up, anhydrous process, lack of organic solvents, lower temperature and residence time of the drug carrier mix, and improved content homogeneity.

7.3. Semisolids Casting

Water-soluble polymer solution that forms films is ready The resulting solution is mixed with an acid-insoluble polymer solution (such as cellulose acetate butyrate or phthalate). The right amount of plasticizer is applied to achieve the desired mass of gel. Using heat-controlled drums, the gel mass is finally molded into the films or ribbons. The film should have a thickness of between 0.015 and 0.05 inches. The acid insoluble polymer to film-forming polymer ratio need to be.

7.4. Solid Dispersion Extrusion

In order to load the medicine, the method entails dispersing the drug solidly within a melted polymer solution. To create a solid dispersion, the medication is dissolved in a suitable liquid solvent and the resulting solution is added to a suitable polymer melt that can be reached below 70°C without the need to remove the liquid solvent. Ultimately, dyes are used to form the solid dispersions into films.

7.5. Rolling method[21]

In rolling method, both the drug solution and film forming polymer solution are mixed thoroughly and the resultant solution or suspension is subjected to the roller. The solution or suspension should have specific rheological consideration. The film is dried on rollers and cut into desired shapes and sizes.

8. EVALUATION PARAMETERS

8.1. Thickness
8.2. Dryness/tack test
8.3. Tensile strength
8.4. Percent elongation
8.5. Tear resistance
8.6. Young's modulus
8.7. Folding endurance
8.8. In vitro disintegration test
8.9. In vitro dissolution studies
8.10. Drug content uniformity
8.11. Surface pH test
8.12. Contact angle
8.13. Transparency
8.14. Scanning electron microscopy
8.15. Percentage moisture loss
8.16. Determination of % yield of buccal patches

8.1. Thickness Test

The thickness of film is measured by micrometer screw gauge or calibrated digital Vernier Calipers. The thickness of film should be in range 5-200 µm.[22] The thickness should be evaluated at five different locations (four corners and one at centre) and it is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film.

8.2. Dryness / Tack test

Tack is the strength with which the film attaches to any piece of paper that is put into contact with the strip, whereas dryness is the quality to measure the solvent or water content present in the film. It has been determined that there are eight distinct stages in the drying process for

films: set-to-touch, dust-free, tack- free, dry-to-touch, dryhard, dry-through, dry to-recoat, and dry print free. These characteristics can currently be measured using many different equipment. This can be accomplished at lab scale by pressing the thumb against the film.[23]

8.3. Tensile strength

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

Tensile strength = Load at failure × 100/Strip thickness × Strip width

8.4. Percent elongation

When stress is applied on a film (2 × 2 cm2) sample it gets stretched, this is referred to strain. Strain is basically the deformation of strip before it gets broken due to stress. It is measured by using hounsfield universal testing machine.[24] Generally elongation of strip increases as the plasticizer content increases. It is calculated by the formula:

% Elongation = Increase in length of strip × 100/Initial length of stri

8.5. Tear resistance[25]

Plastic film or sheeting's tear resistance is a complicated function of its ultimate rupture resistance. The force needed to start tearing is essentially measured using a very modest loading rate of 51 mm (2 in.) /min. The tear resistance value is expressed in Newton's (or pounds-force) and represents the maximum stress or force (which is typically obtained close to the outset of tearing) needed to tear the specimen.

8.6. Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of strip.[26] It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's modulus = Slope × 100/Strip thickness × Cross head speed.

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

7.7. Folding endurance

Film's flexibility is a crucial physical quality required for easy application on the administration site. The strength of the film can be quantitatively measured in terms of folding endurance by simply folding the mouth dissolving film at a 180° angle of the surface at the same layer until it fractures or by folding it three hundred times without breaking. The folding endurance value is calculated as the folding number ofthe film can endure without breaking.[27]

8.9. In vitro disintegration test

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30 s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time.[28] In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates.[29]

8.10. In vitro dissolution studies

Dissolution is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature, and solvent concentration. The standard basket or paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing. The selection of dissolution medium will essentially depend as per the sink conditions and highest dose of API. The temperature of dissolution medium should be maintained at 37 ± 0.5°C and rpm at 50. When the paddle apparatus is employed, it has a disadvantage that oral films have a tendency to float over the dissolution medium. Mashru et al.,[30] used stainless steel wire mesh with sieve opening of approximately 700 µm used to dip salbutamol fast dissolving film inside the dissolution medium.[31,32]

8.11. Drug 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%.[33]

8.12. Surface pH test

The surface pH of fast dissolving strip can cause side effects to the oral mucosa, so it is necessary to evaluate the surface pH of film. The surface pH of film should be 7 or close to neutral. For this purpose, a combined pH electrode can be used. With the help of water, OS was made slightly wet and the pH was measured by bringing electrode in contact with surface of oral film. This study should be done on at least six films of each formulation and their mean ± SD can be calculated.[34] In another method to determine the surface pH, the films are placed on the 1.5%w/v agar gel and then the pH paper are placed on the film, change in color of pH paper gives surface pH of the film.

8.13. Contact angle

Contact angle measurement predicts the wetting behavior, disintegration time, and dissolution of oral film. These measurements are performed with help of goniometer (AB Lorentzen and Wettre, Germany) and the measurements should be done at room temperature. The water used to determine contact angle should be double distilled water. A drop of double distilled water is placed on the surface of dry film.[35] Images of water droplet are recorded within 10 s of deposition by means of digital camera. Digital pictures can be analyzed by

imageJ 1.28v software (NIH, USA) for angle determination.

8.14. Transparency

To determine transparency of oral film, a simple ultraviolet (UV) spectrophotometer can be used. The film specimen is placed on the internal side of spectrophotometer cell. The transparency of films is calculated as follows:

Transparency = (log T600)/b = −€c

Where T600 is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.[36]

8.15. Moisture content

The brittleness and friability of films are impacted by the emoisture content. In short, the product's ingredients control how much moisture is present in a given film. Generally, moisture content testing equipment, the Karl Fisher titration method, or the weighing method used to determine how much moisture is contained in the film. Usually, a pre-weighed film of a certain size is heated to between 100 and 120 °C until it reaches a consistent weight, and the difference in weight indicates the amount or level of moisture contained in the film.

% Moisture content= [(Starting mass - Final mass) 100/Initial weight] used to compute moisture content. The optimal moisture content for a film is 5% or less.6

8.16. Scanning electron microscopy

To study the surface morphology of film between different excipients and drug scanning, electron microscopy can be used. The film sample should be placed in sample holder and at ×1000 magnification, various photomicrographs can be taken using tungsten filament as an electron source.[37]

8.17. Determination of % yield of buccal patches[38]

Percentage yield of buccal patches can be calculated by the following formula:

% yield = Mass of the buccal patches obtained/Total weight of drug and polymer × 100

8.18. Permeation studies

Even though permeability of oral mucosa is 4-1000 times greater than that of skin, permeation studies should be carried out. To study the permeability, modified Franz diffusion cell can be used along with porcine buccal mucosa. The Franz diffusion cell consists of a donor and a receptor compartment. In between the two compartments, mucosa is mounted and the size of the mucosa should be of the same size as that of the head of receptor compartment. The receptor compartment is filled with buffer and maintained at 37 ± 0.2°C and to maintain thermodynamics a magnetic bead stirring at a speed of 50 rpm is used. A film specimen moistened with a few drops of simulated saliva should be kept in contact with mucosal surface. The donor compartment should consist of 1 ml simulated saliva fluid of pH 6.8. At particular interval, samples are withdrawn and replaced by same amount of fresh medium. By suitable analytical method, percentage of drug permeated can be determined.[39]

8.19. Stability study

Stability study should be carried out according to the International Conference on Harmonization (ICH) guidelines. The prepared formulation was wrapped in a special way. Firstly, it was wrapped in a butter paper then above it an aluminum foil was wrapped and the packing should be placed in an aluminum pouch and make it heat sealed. The storage conditions at which formulations are kept should be 30°C/60% relative humidity (RH) and 40°C/75% RH. After 3 months, the films were evaluated for drug content, disintegration time, and physical appearance observation.[40]

9. Storage and packaging of OS

Fast dissolving strips can be packed using single pouches, blister card with multiple units, multiple-unit dispenser, and continuous roll dispenser. There are certain patented packaging systems for fast dissolving films such as Rapidcard by Labtec and Core-peel by Amcor flexible. The rapid card is of same size as a credit card and holds three films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics:

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper-resistant requirement
- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product tastes or odors.[41]

Foil, paper or plastic pouches: The flexible pouch is a packaging concept capable of providing not only a package that is temper- resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminum pouches.

Single pouch and Aluminum pouch: Soluble film drug delivery pouch is a peelable pouch for “quick dissolve” soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutriceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

Blister card with multiple units: The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat – softening a sheet of thermoplastic resin and vaccum-drawing the softened sheet of plastic into a contoured mold. After cooling the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi –rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.[41]

Barrier Films: Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. Several materials may be used to provide moisture protection such as Polychlorotrifluoroethylene (PCTFE) film, Polypropylene.

Polypropylene does not stress crack under any conditions. It is an excellent gas and vapour barrier. Lack of clarity is still a drawback.

9.1 List of some marketed products available as fast dissolving strips

Table No. 4: List of some marketed products available as fast dissolving strips.

Product	API	Manufacture	Uses
Listerine	Cool mint	Pfizer, Inc.	Mouth ulcer
Brenadyl	Diphenhydramine HCL	Pfizer	Antiallergic
Suppress	Menthol	Innozen , Inc .	Cough suppreserent
Klonopin wafers	Clonazepam	Solvay pharmacuticals	Antianxiety
Theraflu	Dextormethrophan	Novartis	Antiallergic
Orajel	Methollpectin	Del	Mouth ulcer
Gas-x	Simethicone	Novartis	Antiflatuating
Cholrasepic	Benzocaine\ methol	Prestige	Sore through
Sudafed PE	phenylepinephrine	Wolters Kluwer health, Inc.	Congestion
Triminic	Diphenhyadramine	Novartis	Antiallergic

9.2 Recent Patent Of fast Dissolving Film

Table No. 5: Recent Patent Of Fast Dissolving Film.

Title	**Patent number**	**Inventor**	***Issued***	**Assignee**
Water soluble film for oral administration with instant wettability	5,948,430	*Zerbe.et.af.*	Sep 7,1999	LTS Lohman Therapy-system GmbH
Biodegradable film for delivery of pharmaceutical compound of mucosal surface	6159498	Tapolsky et af.	Dec 12,2000	-
Fast dissolving orally consumable film containing sweetener	2003,021 1136	Lori et at.	Nov 13,2003	Warner Lambert company LLC
Fast dissolving film for oral administration of drug	2004,0208931	Friend et af.	Oct 21,2004	William squire,Esq.
Fast dissolving consumable films containing a modified starch for improved heat and moisture resistance	2004,0247646	David et af.	Dec. 9, 2004	Prizer,Inc.
Fast dissolving orally consumable films	7,025,983	Leung et af.	April 11, 2006	Warner Lambert company LLC
Dissolving thin film xanthone supplement	7182964 82	Kupper et af.	Feb 27, 2007	-
Thin film strips	7,241,411	Berry et af.	Jul 10,2007	Acupac packaging, NC.
Disintegrable film for diagnostic devices	7,470,397	Meathrel et af.	Dec 30,2008	Adhesive research,Inc.
Pharmaceutical carrier devices suitable for delivery of pharmaceutical compound to mucosal surface	757901982	Tapolsky	Aug 25,2009	-
Film comprising nitroglycerin	20100215774	Maibach and Todd wern et af.	Aug 26,2010	-
Dissolvable tobacco film strips and method of making the same	794629682	Wern et af.	May 24,2011	-

10. CONCLUSION

- ✓ MDF formulations are a promising dosage form for treating diseases and disorders,
- ✓ representing a unique approach in the pharmaceutical industry.
- ✓ Novel formulations have increased patient compliance, acceptance, safety, and effectiveness compared to standard formulations.
- ✓ MDF has several benefits and leads to enhanced therapeutic outcomes. These formulations are currently only available for certain disorders, but their importance suggests that other diseases could be handled using film formulations with appropriate API
- ✓ Key advantages of MDFs include precise dosing, portability, and avoidance of first-pass metabolism,

making them ideal for both systemic and local drug delivery. However, challenges like limited drug loading capacity, taste masking, and ensuring film uniformity and mechanical integrity require optimization during formulation development.

- ✓ This review highlights the critical aspects of MDFs, including their formulation, manufacturing techniques, evaluation parameters, and applications. Recent advancements, such as the use of nanotechnology and bio adhesive polymers, have expanded the scope of MDFs for delivering a wide range of therapeutic agents. As a patient-friendly alternative, MDFs hold great promise for improving medication adherence and therapeutic outcomes. Further research is warranted to overcome existing limitations and explore novel applications.

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