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Review Article

Oral Thin Films: A Modern Frontier in Drug Delivery Systems

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Abstract

Oral thin films (OTFs) are gaining popularity in the pharmaceutical industry for their advantages over traditional oral dosage forms, especially for patients with swallowing difficulties, such as children and the elderly. OTFs provide a discreet, convenient, and fast-acting method of drug administration. They dissolve quickly in saliva, enabling rapid absorption through the oral mucosa, bypassing first-pass metabolism and enhancing bioavailability, which can reduce required doses and side effects. OTFs are particularly useful for poorly soluble drugs and allow for precise dosing, making them ideal for pediatric patients. They can also mask unpleasant tastes, improving patient acceptance. Research on OTFs is expanding, with innovations like pH-sensitive films, micro-pellet-loaded films, and the potential for delivering vaccines and probiotics. The OTF market is projected to reach $7.65 billion by 2028, growing at a 13.6% CAGR. Future developments focus on personalized OTFs, made possible by printing technologies like inkjet and 3D printing, offering tailored dosing and drug combinations. OTFs hold great promise to revolutionize drug delivery, benefiting both patients and healthcare providers.

Key words: Oral thin film, Pediatric and geriatric drug dosing, market growth of OTF, Technologies of preparation of film

1. Introduction

Although oral drug distribution is convenient, it can be challenging for certain populations, including pediatrics, the elderly, and those with dysphagia. These individuals often face difficulties swallowing traditional dosage forms like tablets and capsules. Even fast-dissolving tablets carry a risk of choking and lack universal acceptability. To address these issues, oral fast-dissolving films (OFDFs) have emerged as an innovative alternative. OFDFs are thin, polymer-based films that dissolve quickly on the tongue, making them easy to administer without water or chewing. This technology enhances patient compliance, particularly in elderly patients managing multiple medications and those with conditions such as Alzheimer's, Parkinson's, and schizophrenia. OFDFs are also beneficial for pediatric patients, offering a safe and easily administered alternative to traditional forms.[1] OTF becomes further popular for colorful, potent cures in discrepancy to immediate-release ODT. With ODT, healthcare professionals are facing non-compliance in the treatment of pediatric and senior cases. ODT is designed for quick disintegration in the mouth, but fear of choking remains a concern for some patients. On the other hand, OTF expression can improve patient compliance by addressing swallowing issues. Senior patients often take multiple medications per day. The convenience of administering lozenge forms is crucial for patients with Alzheimer's, bipolar disorder, migraines, Parkinson's disease, and schizophrenia. Among all types of lozenge forms, OTF is largely accepted due to its own advantages along with ease of oral delivery of colorful medicines (e.g., anesthetics, antihistamines, anti-asthmatics, cardiovascular medicines, neuroleptics, and medicines for erectile dysfunction [2].Recent innovations have expanded OFDF capabilities, including the integration of nanotechnology to increase the solubility and bioavailability of weakly water-soluble medicines; for instance, nanonization and cyclodextrin inclusion complexes are utilized to enhance dissolution rates for BCS Class II drugs [3, 4]

Multi-layered films and mucoadhesive formulations further allow controlled release and targeted delivery, ensuring therapeutic efficiency and patient adherence. [5, 6] Personalized OFDFs, particularly for pediatric cases, address dosing inaccuracies associated with splitting tablets or liquid formulations. By producing films in hospital settings under GMP standards, tailored dosages

can be provided, improving therapeutic outcomes.[7] With advancements in material science and manufacturing processes, OFDFs are poised to revolutionize oral drug delivery, offering a user-friendly, efficient, and versatile platform for diverse patient needs.

1.1 Advantages of oral film:

1 Fast disintegration within seconds and quick onset of action

2 Easy administration

3 No fear of chocking like orally disintegrating tablet

4 Suitable for children and geriatric patients, bedridden individuals, and those with dysphagia, Parkinson's disease, mucositis or vomit.

5 Accurate dosing can be achieved

6 Improve the bioavailability of drugs having first-pass metabolism.

7 Thin and can be administered without water

8 Easy to transport and flexible, robust in nature.[7]

Table 1: Market and Clinical Film Advantages

Market Advantages	Clinical Advantages
Extending Revenue Life Cycles	Improved bioavailability of medicines with high first- pass metabolism.
Marketing Exclusivity and Increased Revenue	Reduced Side Effects by lowering the required dose, oral films may also contribute to a reduction in side effects.
Discourage tampering and reduce the dangers associated with misuse and abuse of certain prescription medications.	Faster onset of action Drugs absorbed through the oral mucosa have a faster onset of action, making oral films ideal for therapies that require quick results. [8]

2. Formulation Strategies for the Preparation of Mucoadhesive and Orodispersible Film

2.1 Hot melt extrusion technique:

Hot melt extrusion uniformly mixes drugs with carriers in a molten state, forming filaments or powders to enhance drug solubility and bioavailability. It is widely used for oral films and is environmentally friendly due to the absence of organic solvents.[9] Hot melt extrusion uniformly mixes drugs with carriers in a molten state, forming filaments or powders to enhance drug solubility and bioavailability. It is widely used for oral films and is environmentally friendly due to the absence of organic solvents.

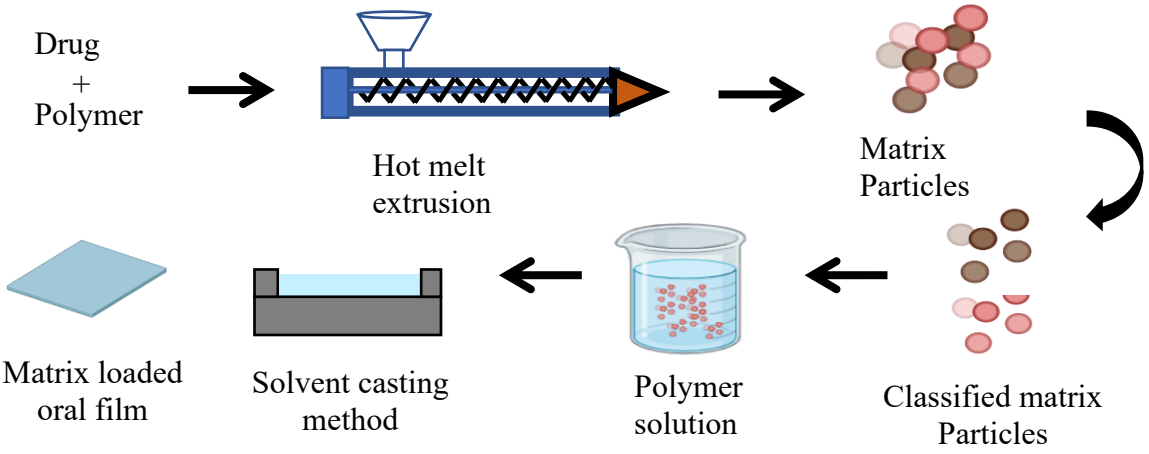

Figure 1 Diagrammatic Representation Hot melt extrusion

2.2 Electrospinning method:

Electrospinning uses an electric field to create nanofibers from polymer solutions, forming non-woven mats for drug delivery. Chitosan/pullulan FDOFs were prepared by charging polymer solutions and ejecting them onto a grounded drum. **(fig 2)** The ratio of chitosan to pullulan in the solution varied, and the solutions were characterized by their viscosity, conductivity, and surface tension. Scanning electron microscopy was then used for examination of the morphology of the resulting nanofibers[10]. Multilayer films, such as ethyl cellulose/gelatin nanofibrous films, were fabricated by sequential electrospinning to control drug release. Other applications include mucoadhesive buccal patches with dual layers for unidirectional drug delivery, combining PVP/Eudragit RS 100 with a protective polycaprolactone backing.[11]

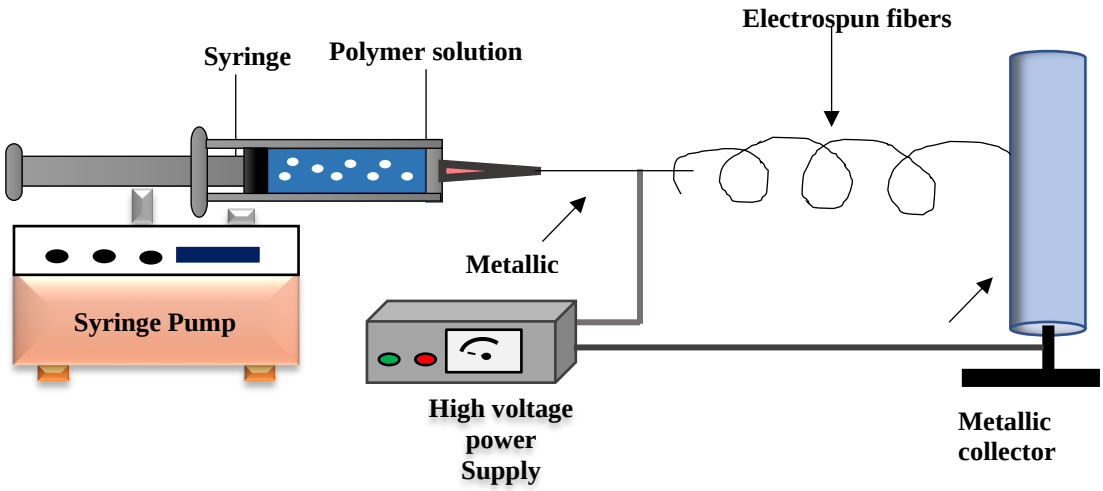

Figure 2 Diagrammatic Representation Electrospinning method

2.3 Printing technology:

Printing technology refers to processes that use computer-aided design (CAD) to create three-dimensional objects by depositing materials layer-by-layer **(fig. 3).** This technology can be used to create a variety of objects, including oral films for drug delivery. This method involves depositing precise amounts of a liquid formulation containing the API onto a substrate. The article also describes drop-on-demand printing as an alternative method for depositing molten formulations onto a substrate to create ODFs [12] The fused deposition modeling (FDM) 3D printing is another way of creating mucoadhesive buccal films for unidirectional drug release. The process starts with creating drug-loaded filaments via hot melt extrusion using PVA, xylitol, and diclofenac sodium, with or without chitosan. A MakerBot Replicator 2X FDM printer is used to print these filaments into four-layered films. For films with backing layers, either ethyl cellulose is 3D printed on top or commercial wafer edible sheets are manually applied to the printing platform [13]. A combined FDM and inkjet method was prepared by Fatouros et al. incorporating heat-sensitive drugs like lidocaine into HPMC-based buccal films with ethyl cellulose backing for unidirectional drug release. [14]

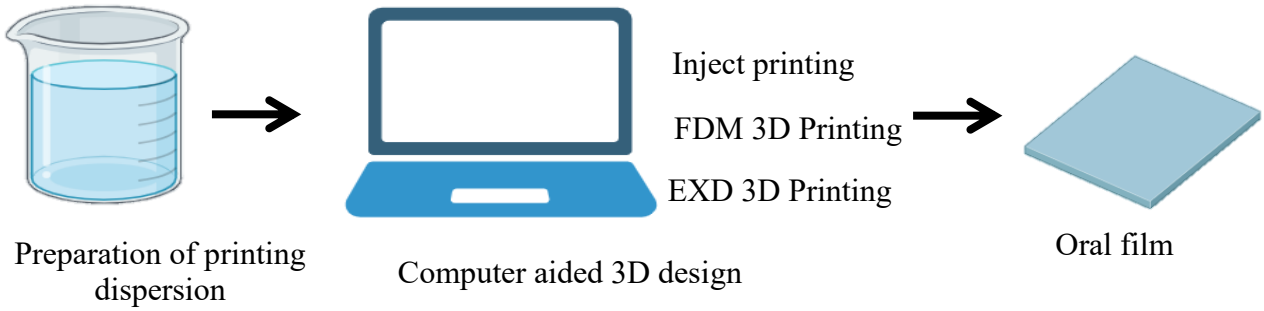

Figure 3 Diagrammatic Representation Printing Technology

2.5 Solvent casting method:

Solvent casting is a widely used technique for producing films, especially in the pharmaceutical industry for creating orodispersible films (ODFs). **(fig 4)**

This method involves dissolving the polymer and the active pharmaceutical ingredient (API) in a suitable solvent. The resulting solution, called the film casting mass, is then cast onto a substrate like a PET (polyethylene terephthalate) foil. The film is dried in a controlled environment, typically an oven, to allow the solvent to evaporate. As the solvent evaporates, the polymer and API molecules come closer together, eventually solidifying into a thin, uniform film. The properties of the resulting film, like its porosity, time of disintegration, and mechanical strength, depend on the formulation of the casting solution and the drying conditions. This method is particularly beneficial for heat-sensitive drugs and excipients as it avoids the high temperatures involved in other film preparation techniques like hot-melt extrusion[15] However, the solvent casting method has limitations, including challenges in scaling up, residual solvent concerns, environmental impact, and difficulties in achieving high drug loads due to solubility and crystallization issues. [16]

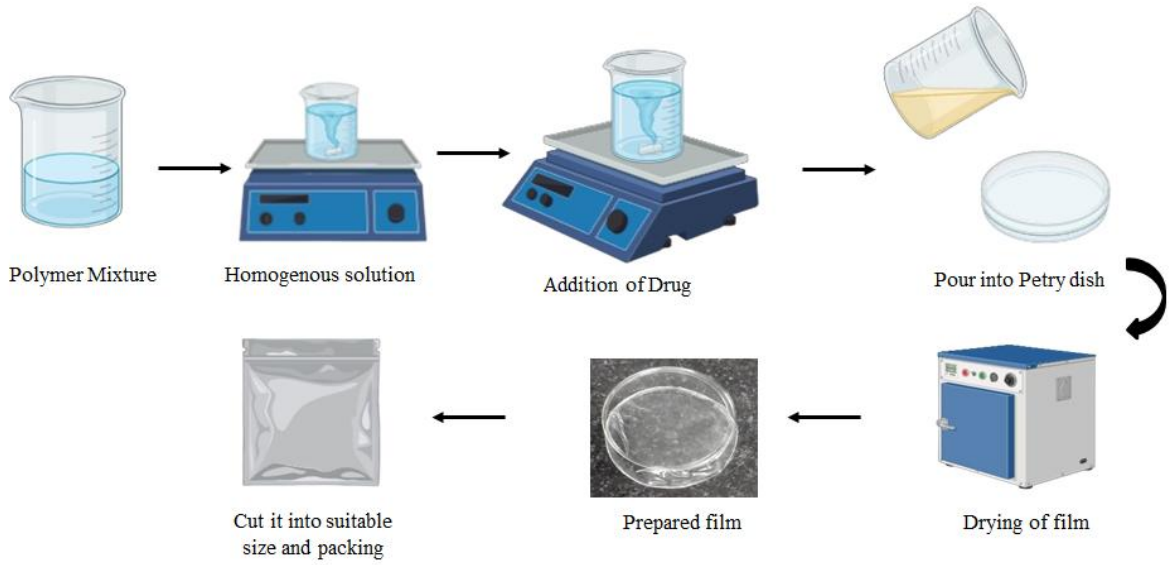

Figure 4: Diagrammatic Representation Solvent casting method

3. EMERGING TREND OF ORAL FILM

Oral dispersible films are gaining more importance nowadays due to their versatile application in the delivery of vaccines, protein peptides, and herbal extracts, which are discussed in further sections:

3.1 Vaccine:

Oral administration of vaccines is challenging because of their low inherent stability and degradation and metabolism resulting in poor bioavailability.[17]Tian and coworkers developed orodispersible films (ODFs) using trehalose and pullulan to stabilize therapeutic proteins like β-galactosidase, with freeze-drying enhancing process stability and air-drying improving storage stability.[18] Remarkably, the COVID-19 pandemic emphasized the need for innovative vaccine delivery methods. While most COVID-19 vaccines are intramuscular and require cold storage, increasing costs and limiting use in tropical regions, oral recombinant vaccines like Vaxart's pill in 2021 showed promise in phase II trials. ODFs offer a patient-friendly, cost-effective alternative for vaccine delivery, addressing storage, transport, and injection-related challenges.[19]

3.2 Probiotics:

Probiotics like Streptococcus salivarius have potential in managing oral health issues, including dental caries caused by Streptococcus mutans. Orodispersible films (ODFs) with S. salivarius and xylitol, fabricated using inkjet printing, provide localized delivery, bypassing harsh gastric conditions. These films reduce S. mutans populations in vitro, with xylitol inhibiting bacterial metabolism and S. salivarius preserving tooth phosphate integrity.[20] Saha and coworkers formulated ODFs with CMC polymer to deliver Lactobacillus fermentum for periodontitis treatment. Advances in techniques have improved probiotic loading and prolonged release, enhancing antifungal and antibacterial efficacy. S. salivarius-xylitol ODFs achieved a 2.86-log reduction in S. mutans numbers, demonstrating strong antibacterial activity. [21]

3.3 Herbal extracts:

The natural and herbal pharmaceuticals are gaining constant interest nowadays by researchers due to their extensive pharmacological effects, including anti-inflammatory and antioxidant activity such as curcumin [22]. Curcumin oral films offer several advantages for drug delivery, particularly for treating oral diseases. Indonesian oral films infused with traditional herbal extracts (Jamu) offer a flexible, intraoral drug delivery method, bypassing swallowing and absorption issues. Utilizing medicinal plants like *Lagerstroemia speciosa* for diabetes and *Phyllanthus niruri* for immunity, these films enable targeted treatment. Tailored formulations optimize delivery, though extract load limitations may necessitate larger film sizes for some therapies.

Nguyen and coworkers have prepared an ODF loading with Panax notoginseng showing high stability in an acidic medium and fast disintegration in vivo release. The stability of herbal extracts can be maintained in ODF with ease of administration in elderly people and those with chronic treatment of certain diseases. [23]

3.4 Personalized ODF:

Personalized ODFs address the limitations of adult-formulated medications, ensuring suitability for pediatric use. They offer dose flexibility, allowing precise adjustments based on a child's weight, age, and medical needs. Given children's unique pharmacokinetics, ODFs enhance compliance by easing administration and overcoming swallowing difficulties. Taste-masking, flavors, and colors improve palatability and acceptance among pediatric patients. This approach enables safe, effective, and patient-centric drug delivery tailored to children's needs.[24]

Salma et al. have developed a personalized antifungal oral film of atorvastatin that has enhanced antifungal efficacy, improved bioavailability, and anti-inflammatory effect. The film was developed with atorvastatin a cholesterol-lowering drug with antifungal activity. The formulation encapsulated with propylene glycol was

then incorporated into 3D-printed mucoadhesive film composed of chitosan, PVA, and HPMC and designed to provide controlled drug release and adhere to oral mucosa.[25]

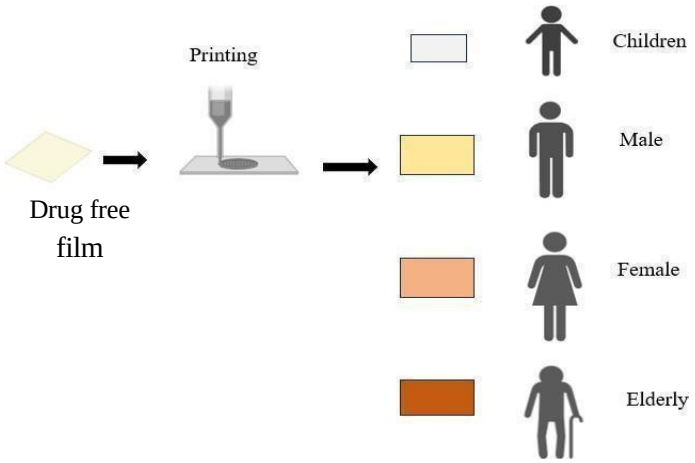

Figure 5: Production of oral disintegration films on demand using a printing technology that takes into account the requirements of various patients.

4 Recent advances in oral film

4.1 pH and sugar sensitive layer by layer thin films

pH- and sugar-sensitive layer-by-layer thin films are the films developed for controlled drug release. pH-sensitive films use weak polyelectrolytes or hydrogen-bonding polymers, with permeability controlled by environmental pH. Sugar-sensitive films incorporate glucose oxidase, lectin, or phenylboronic acid derivatives, which bind sugars to form charged complexes, altering film properties. A major challenge is optimizing sensitivity under physiological conditions.[26]

4.2 Nanoparticle-loaded oral film:

Nanoparticle-loaded ODFs enhance drug delivery by incorporating nanoparticles into fast-dissolving films, improving solubility and bioavailability of poorly soluble APIs (BCS II & IV). By reducing particle size, nanoparticles increase surface area, accelerate dissolution, and protect APIs from degradation, ensuring better therapeutic effects.[27]Targeted drug delivery to specific tissues or organs, Sustained or extended release of the drug, reducing dosing frequency and improving patient compliance, and improved taste masking, making the medication more palatable, especially for pediatric patients. The sublingual film containing nanoparticles of poorly water-soluble drugs like domperidone was prepared to get quick disintegration and rapid onset of action in case of nausea and vomiting produced by chemotherapy, migraine, headache, and other [28] The film was prepared to contain lipid nanoparticles for poorly water-soluble drugs to improve oral bioavailability of BCS class II and IV drugs.[29]

4.3 Micropellete-loaded oral film

Micro-pellet-loaded oral films (ODFs) combine rapid disintegration with controlled drug release by embedding coated drug-loaded micropellets into a film matrix. These micropellets remain intact after film dissolution, allowing prolonged drug release while minimizing dose dumping. The coating and drug amount can be tailored for desired release profiles, offering improved stability, protection, and safer delivery, especially for patients with swallowing difficulties.[30] Isabell Speer incorporated diclofenac-loaded micro pellets in the oral film by using the spheronization technique. The fast-disintegrating microcrystalline cellulose pellets were prepared to enhance the dissolution of poorly soluble indomethacin enhancing its solubility[31]

4.4 Cyclodextrin -based oral film

Cyclodextrins are naturally occurring cyclic oligosaccharides typically composed of six, seven, or eight glucose units linked together in a ring structure and contain a hydrophobic inner cavity and hydrophilic outer surface. The primary purpose of using cyclodextrin in drug delivery systems is to enhance the solubility, bioavailability, and stability of drugs.[32]Cyclodextrin enhances drug solubility in liposomes, increases loading capacity, protects against degradation, and enables sustained release for prolonged therapeutic effects [33].

5. Oral fast dissolving film available in market:

Table 2: Oral fast dissolving film available in market

Trade name	API	Polymer
OTC Products [34, 35]		
Listerine	Menthol	Pullulan
Sudafed PE	Phenylephrine	Maltodextrin carrageen
Gas -X Thin strip	Simethicone	Maltodextrin HPMC
Theraflu® Day Time Thin Strips	Dextromethorphan Diphenhydramine	Hypromellose Maltodextrin
Suppress cough strips	menthol	Carrageen pectin sodium alginate
Chloraseptic® Sore Throat Relief Strips	Benzocaine	Corn starch
Pedia-Lax™ Quick Dissolve Strip	Sennoside	HPMC
Benadryl® Allergy Quick Dissolve Strips (McNeill-PPC)	Diphenhydramine	Carrageen Pullulan
Prescribed Products [36]		
Sildenafil Orodispersible Film	Sildenafil	Maltodextrin
Zuplenz®	Ondansetron	HHPMC
Risperidone HEXAL	Risperidone	HHPMC Maltodextrin

6. Future prospective and market reports of oral film:

Fast-dissolving oral films (FDOFs) are poised to become increasingly important in the pharmaceutical industry due to their numerous advantages over conventional oral dosage forms and a robust research and development pipeline. As the sources explain, FDOFs address the limitations of traditional medications, offering enhanced patient compliance, improved bioavailability, and greater convenience. The enhanced bioavailability is achieved by rapid drug absorption through the oral mucosa, bypassing the first-pass metabolism in the liver and potentially leading to quicker therapeutic effects. The discreet nature and ease of administration of FDOFs make them particularly attractive for patients who struggle with swallowing traditional pills, such as pediatric, geriatric, and mentally disabled individuals. The sources further emphasize that FDOFs represent an opportunity for pharmaceutical companies to differentiate their products, extend the patent life of existing medications, and expand into new markets. As the technology continues to advance, the sources anticipate an expansion of FDOF applications beyond conventional drugs to include hormones, vaccines, and other therapeutic modalities. Despite the current limited availability of prescription FDOFs, a number of key players, including MonoSol Rx, Applied Pharma Research/Labtech GmbH, Bio Delivery Sciences, and NAL Pharma, are actively developing FDOF technologies and partnering with pharmaceutical companies to bring these innovative products to market. The US FDA has already established clear regulatory pathways, including ANDA for bioequivalent products and 505(b)(2) for novel dosage forms, paving the way for wider adoption of FDOFs in the coming years [37]. The oral film global market report shows that the OTF market size has grown rapidly in recent years. It will grow from $4.07 billion in 2023 to $4.6 billion in 2024 at a compound annual growth rate of 13.0%. The growth in the historic period can be attributed to patient compliance, pediatric and geriatric patients, rapid drug delivery, chronic disease, and over-the-counter medications.

The OTF market size is expected to see rapid growth in the next few years; it will grow from $7.65 billion in 2028 at a compound annual growth rate of 13.6%.

7. Components of oral film

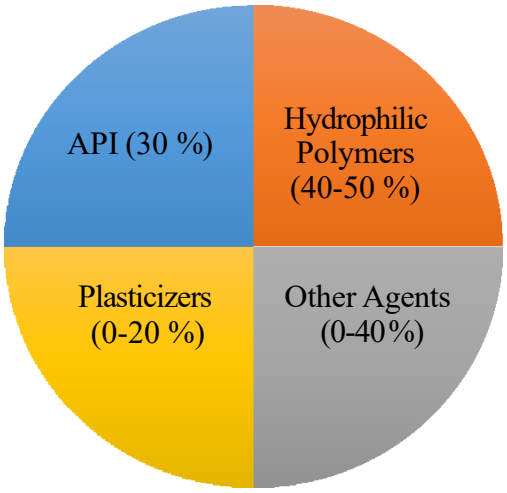

Figure 6: Ingredients used in oral film

7.1 Active Pharmaceutical agents:

The API is the drug or active substance that provides the therapeutic effect. The amount of API that can be incorporated into an oral film is typically limited, with a maximum of around 30 mg. However, films have the

potential to load APIs up to 50% of the unit dose mass [38]

Ideal characteristics of drug that can be incorporated in oral films are:

- Drug dose should be low.
- It must be palatable.
- It is having a smaller molecular weight.
- It must be soluble and stable in saliva [39].
- It should be partially unionized at the pH of the oral cavity.
- It should have the ability to permeate through the mucosa of the oral cavity [40].

Table 3: List of few drugs that can be incorporated in oral film [40]

API	Category	Dose (mg)
Nicotine	Smoking cessation	1-15
Glyceryl trinitrate	Vasodilator	0.3-0.6
Zolmitriptan	Antimigraine	2.5
Loratadine	Antihistaminic	5-10
Desloratidine	Antihistaminic	5
Diphenhydramine HCL	Antihistaminic	25.0
Loperamide	Antidiarrheal	2.0
Famotidine	Antacid	10
Flurazepam	Anxiolytic	15-30
Chlorpheniramine maleate	Antihistaminic	4
Acrivastine	Antihistaminic	8
Oxycodone	Opioid analgesic	2.5-10
Dicyclomine	Muscle relaxant	25
Omeprazole	Proton pump inhibitor	10-20
Cetirizine	Antihistaminic	5-10
Ketoprofen	Anti-inflammatory	12.5-25
Levocetrizine ,Loratadine	Antihistaminic	5-10
Ketorolac Indomethacin Valdecoxib Piroxicam	NSAID	10,25,10,20
Mirtazapine	Antidepressant	15,30,45
Buspirone	Anxiolytic	5,10
Carvedilol	Beta blocker	3

7.2 Polymers

Polymers are a set of monomers that can be employed individually or in combination to achieve desired strip qualities. Polymers play a crucial role in film preparation due to their impact on the disintegration time and strength of the film.[41] Because the strip-forming polymer (which forms the platform for the OS) is the most important and primary component of the OS, at least 45% w/w of polymer should normally be present based on the total weight of dry OS [42]. Typically, 60-65% water-soluble polymer is ideal for creating OS with specified qualities[43]. As a polymer emulsion loses water, capillary pressure pushes particles together, causing them to deform and merge into a film. The minimum film formation temperature is where the polymer's modulus allows deformation under this pressure [44].

Ideal characteristics of polymers used in oral film:

- The polymer used should be non-toxic, non-irritating, and free of leachable impurities.
- The material should have good wetting and spreading properties.
- The polymer should have sufficient peel, shear, and tensile strengths.
- The polymer should be freely available and affordable.
- It should have a long shelf life.[45]

Polymers used in preparation of mucoadhesive film

Table 4: Polymers used in preparation of mucoadhesive

Polymers	formula	properties	Advantages	Ref
Polyacrylates (e.g., Carbopol®, Noveon®)	C3H4O2 *n*	Possess carboxylic groups that interact with mucin's oligosaccharide chain physical entanglement with mucus layers further enhances adhesion Swelling upon hydration can pose challenges for patient compliance.	Excellent, mucoadhesive properties due to strong hydrogen bonding with Mucin Form transparent, easily modified gel networks Non-toxic and considered safe (GRAS status) for oral use.	46,47, 48,49,50
Hyaluronic acid (HA)	C8H13NO7 *n*	Unbranched polysaccharides with repeating unit of D glucuronic acid and N-acetyl D glucosamine assumes an expanded coil structure in solution	Enhances drug penetration strong adhesion to buccal mucosa particularly at lower molecular weights forms a strengthen mucus layer upon interpretation with mucus	51, 52,53,54
Chitosan	GlcNlcNAc *n*	Can form complexes with drugs to enhance solubility and mucosadhesion mucoadhesive properties can be weakened by chemical cross linkers molecular weight confirmation and degree of acetylation influence its mucoadhesive behavior.	Biocompatible and biodegradable positively charged amines interact with negatively charged salicylic acid residues in mucin.	55,56, 57,58
Cellulose Derivatives e.g. (HEC, HPMC, HPC, CMC)	C6H10O5N	Non-ionic derivatives like HPMC have moderate mucoadhesive properties Anionic CMC offers hydrogen bonding ability for better adhesion.	Wide range of available derivatives with varying properties CMC exhibits the best mucoadhesive properties among cellulose derivatives.	59
Alginate	$C_6H_7NaO_6$ (sodium alginate)	Linear Polysaccharide composed of Mannuronic acid (M) and guluronic acid (G) units High molecular weight alginate can bridge distant mucin sites and contract the protein	Excellent bioadhesive properties Forms microparticles suitable for Prolonged drug release	60
Pectin	$C_6H_{10}O_7$	Pectin is a natural, biodegradable, and mucoadhesive polysaccharide with gel-forming, pH-sensitive, and controlled drug release properties	Superior mucoadhesion at low molecular weights	61,62,63
Gelatin	$C_6H_{12}O_6$	Natural polymer often used in combination with other mucoadhesive agents	Forms strong mucoadhesive bonds between combined with other polyemers like HPC, HPMC and NaCMC	64
Polyvinylp-yrrolidone (PVP)	*C6H9NO)n*	Poor mucoadhesive properties on its own	Can enhance mucoadhesive properties of other polymer when blended	64
Natural polymer				
Pullulan	*C*20*H*36*O*16	Nonionic non hygroscopic nontoxic non mutagenic and noncarcinogenic biodegradableble. Odorless, tasteless, soluble in hot and cold water and dilute alkali Lower viscosity compared to other biopolymers	Good film-forming properties often blended with other polymers like HPMC; Pectin, Maltodextrin	65,66,67
Maltodextrin	*C*12*H*22*O*11	Non sweet, nutritious, oligosaccharide good film former, odorless, low hygroscopicity. Good solubility in water,	Excellent carrier for active compounds forms films with good mechanical properties	68,69,70

		poorly soluble in anhydrous alcohol (DE) significantly impacts film properties, with lower DE resulting in higher tensile strength and faster disintegration.	and fast disintegration often blended with HPMC to further enhance properties	
Starch	$(C6H10O5)n$	Abundant polysaccharide composed of amylose and amylopectin semi crystalline nature may require modification for improved solubility and mechanical properties source of starch	Forms transperant, odorless, tasteless and biodegradable films or pregelatinized starch are particularly suitable for ODF offering fast disintegration and good mechanical properties often blended with gelatin or HPMC to optimize properties	[71,72]
Hydrolyzed Collagen	$CO(NH2)2$	Derived from collagen via enzymatic hydrolysis low viscosity solution, high solubility, antioxidant, antimicrobial not suitable for film formation alone due to low molecular weight	Enhances flexibility and hydrophilicity when blended with other polymers like gelatin	[73, 74]

7.3 Plasticizers

Plasticizers are essential additives in films, enhancing polymer flexibility, durability, and processability by lowering the glass transition temperature (Tg), making films less brittle and more pliable. The selection of a plasticizer depends on its compatibility with the polymer, often following the "like dissolves like" principle. Hydrophilic polymers with hydroxyl groups are plasticized by hydrophilic agents like glycerol and polyethylene glycols, while less polar polymers, such as cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose phthalate (HPMCP), are better suited for organic esters like citrates and phthalates. Plasticizer concentration, typically 0–20% w/w of dry polymer weight, is crucial to avoid issues like plasticizer migration ("blushing"). [47, 75]The plasticizer should permanently enhance flexibility and decrease Tg within the range of 40–60°C for non-aqueous systems and below 75°C for aqueous systems [85, 86]. Certain drugs, such as ibuprofen with Eudragit RS 30 D, act as plasticizers, reducing Tg via hydrogen bonding and forming smooth films[76]. Plasticization mechanisms include internal (chemical interaction, potentially altering drug release, e.g., PEG 4000 and phenobarbital) and external (no chemical changes, preferred by formulators) methods.[77]

7.4 Miscellaneous components:

7.4.1 Saliva stimulating agent

Saliva-stimulating agents enhance the disintegration of fast-dissolving oral strips by increasing saliva production. Acids like citric, malic, lactic, ascorbic, and tartaric acid (2–6%) are effective stimulants, with citric acid being the most preferred. Sweeteners, both natural (e.g., glucose, fructose) and artificial, also aid in salivary stimulation, with artificial sweeteners offering lower required concentrations and reduced dental caries risk [78].

7.4.2 Sweetening agents:

Sweeteners are vital in food and pharmaceutical products designed to dissolve or disintegrate in the oral cavity, especially for pediatric formulations including natural (glucose, fructose, sucrose) and artificial (acesulfame-K, sucralose, neotame) types.[79] Sucralose is 600–1000 times sweeter than sucrose, aspartame 200 times, and saccharin sodium 300–500 times, with minimal impact on ODF flexibility.[80]

7.4.3 Flavoring Agent:

Flavoring agents in ODFs mask API bitterness with FDA-approved options like sweet, sour, and mint flavors. A study found mint, licorice, and sucralose effectively masked diclofenac sodium's bitterness, with electronic tongues aiding taste analysis. [81]

7.4.4 Super disintegrating agent:

Surfactants in ODFs aid in dispersion, wetting, and solubilization, ensuring rapid disintegration and drug release for patients with swallowing difficulties. Common surfactants include benzalkonium chloride, tweens, and sodium lauryl sulfate, while poloxamer 407 is frequently used for its performance-enhancing properties. Selection depends on the drug, disintegration time, and excipient compatibility.[82]

8.Characterizations of film:

8.1 Chemical stability studies:

These studies are conducted to determine any potential interactions among excipients in the film. Techniques such as Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction are commonly employed for compatibility [83].

8.2 Thickness Measurement:

The film's thickness is an important parameter that can be measured using an electronic digital micrometer, digital Vernier caliper, or micro screw gauge. To ensure uniformity, the film is measured at different locations, including the corners and the center.[84] Usually three readings are taken from all batches, and their average is calculated. The film's uniformity is directly proportional to the dose accuracy of the film .[85]

8.3 Swelling study:

The swelling ability of the film is evaluated by placing it on an agar plate and incubating it at 37 ± 2°C. The increase in diameter and weight of the film is monitored at specific time intervals (1-5 hours) to determine its swelling capacity.[86]

$$\% \text{ Swellability} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

8.4 Tensile strength (TS):

Tensile strength is defined as the maximum stress that a material can repel while being stretched or pulled ahead before breaking. Tensile strength is a critical quality control parameter for oral films as it indicates the ability of the film to withstand handling and transportation without damage. It is important for manufacturers to know the optimal formulation that balances tensile strength with other desired properties, such as flexibility and disintegration time.[87]

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}} \times 100$$

8.5 Factors affecting are:

- Polymer type and concentration [88]
- Plasticizer content
- Moisture content[89]

8.6 Percent elongation

Percent elongation measures how far a material can extend before breaking. When tension is applied to the strip sample, it stretches, which is known as strain. Generally, elongation of the strip rises as the plasticizer content increases. [90]

$$\% \text{ elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

Percent elongation tends to increase as plasticizer content in the material increases. Materials that are hard and brittle have low percent elongation, while more flexible materials have higher percent elongation.[91]

8.7 Folding endurance:

Folding endurance is defined as the number of times an oral film can be folded at the same place until it breaks. This property is sometimes referred to as flexibility. The number of times the film can be folded without breaking is the folding endurance value. Another way to measure flexibility is to fold film 300 times without breaking it.[90]Folding endurance is an important characteristic of oral films, particularly buccal films. The thin films need to be flexible enough to withstand holding and packaging without being damaged. Folding endurance also impacts patient comfort. Thicker oral films, like some buccal patches on the market, can be inconvenient for the patient if the film is not flexible. [92]

8.8 Disintegration time:

Official pharmacopeias recommend using a disintegration instrument to measure film disintegration time. Film disintegration time varies according to material and formulation, often ranging from 5 to 30 seconds. There are no official guidelines available for determination of disintegration time [93].

There are two ways available to determine the disintegration time of film.

A. Slide frame method:

A drop of distilled water is put onto the film, which is clamped into slide frames and placed in a petri dish. The time it takes for the film to disintegrate is noted.

B. Petri dish method:

A film is positioned over 2 ml of distilled water in a petri dish. The time it takes for the film to totally dissolve is considered the disintegration time. [94]

8.9 Dissolution test:

Dissolution testing for oral films is normally performed using a standard USP dissolution device, such as a basket or paddle device, to establish the rate and degree of drug release from the film. The choice of solvent (typically 900 ml) depends on the drug's solubility and the desired sink conditions, which ensure that the drug dissolves in the medium without reaching saturation. To mimic oral cavity conditions, the temperature is maintained at 37 ± 0.5 °C and the rotation speed is adjusted to 50 rpm. Samples are taken from the dissolving media at regular intervals and tested for drug release using appropriate methods. An analytical technique, frequently spectrophotometry, is used at a specified wavelength [95].

8.10 Drug content /content uniformity:

Drug content evaluation for oral films involves determining the quantity of active pharmaceutical ingredient (API) present in the film to ensure accurate dosing. This is typically done using a standard assay method described in a pharmacopoeia for the specific API. Content uniformity is also assessed by analyzing the API quantity in each film strips, with the acceptable range typically being 85-115%. With standard deviation less than or equal to 6% [96] Ensuring proper drug content and uniformity is critical for product quality and efficacy

8.11 Evaluating Water Content in Oral Films

Water content is a crucial parameter in oral film formulations as it can impact the film's mechanical properties, time of disintegration, and stability. Residual water in the films is typically measured using various methods like Karl Fischer titration, loss on drying, or dynamic vapor

permeability. Excess water content can make films sticky, while too little water can result in brittle films that are prone to damage. The sources also point out that water content can influence disintegration time: lower water content can lead to longer disintegration times because it makes it harder for water to penetrate the polymer matrix [97]

8.12 Surface pH:

The pH of the surface is an important characteristic, as it may irritate the mucosal tissues. The film is immersed in 1.0 milliliter of distilled water with a pH of 6.5 ± 0.05 for

two hours in order to determine the surface pH. For this, a glass tube that has been specially made is utilized. A combination glass electrode is placed close to the film's surface for one minute in order to measure the surface pH. [98]

8.13 Morphology study:

Surface morphology refers to the surface features and structure of a material, and in the case of oral films, it can impact properties like drug release, adhesion, and mechanical behavior. Various microscopy techniques, like scanning electron microscopy (SEM), electron microscopy, and scanning tunneling microscopy, are used to examine the surface morphology of oral films. SEM is the most widely used technique, and it allows researchers to observe characteristics like the size, shape, and number of pores present on the film's surface. Understanding the surface morphology of oral films is important for optimizing their design and performance. [99] Scanning electron microscopy (SEM) reveals changes between the upper and lower sides of films. It also helps to determine the dispersion of API.[100]

8.14 Moisture Uptake in Oral Films

To measure moisture uptake, a film sample is placed in a desiccator for 24 hours, then moved to a desiccator at 84% relative humidity until it reaches a constant weight. The humidity uptake is calculated as the percentage change in weight, representing the quantum of humidity the film absorbs. [101]

$$\text{Moisture uptake} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

8.15 Ex–vivo Permeation Studies:

Ex vivo permeation studies are conducted to evaluate the rate at which a drug permeates through the mucosal membrane from an oral film. These studies utilize a modified Franz diffusion cell, which consists of two compartments: a donor compartment where the oral film is placed and a receptor compartment filled with phosphate buffer (pH 7.4) to simulate physiological conditions. An artificial or animal (typically rabbit) mucosal membrane is positioned between the two compartments. The membrane is allowed to stabilize for one hour before the film is introduced. During the study, samples are periodically withdrawn from the receptor compartment to measure the quantity of drug that is permeable across the membrane, and the withdrawn volume is replaced with fresh buffer. These studies are important to assess the drug's ability to cross the mucosal barrier and reach the systemic circulation, providing insights into the potential bioavailability of the drug from the oral film formulation [102]

8.16 In Vivo Evaluation of Oral Films

In vivo evaluation of buccal films is more insightful than in vitro/ex vivo testing as it provides a better understanding of how the formulations actually behave. These studies are typically employed to evaluate pharmacokinetic characteristics, residence duration, drug release, irritation, absorption, and bioavailability. Residence time is typically evaluated in human subjects by measuring the time it takes for the buccal film to completely detach from the buccal mucosa. Volunteers are typically asked to refrain from eating or drinking during the test. Drug release studies are also conducted in humans by applying the film to the buccal cavity and periodically collecting saliva samples to analyze the amount of drug released. Drug absorption is evaluated in both animal models and humans using direct methods, like collecting blood samples to measure drug concentrations, and indirect methods, like measuring the amount of drug remaining in a perfusion chamber after circulating it through the oral cavity. Bioavailability can then be calculated from this data[103].

Conclusion

Oral fast-dissolving films (ODFs) are gaining prominence in the pharmaceutical industry due to their numerous advantages over traditional oral dosage forms. ODFs offer enhanced patient compliance, improved bioavailability, and greater convenience, especially for dysphagia patients like pediatric, geriatric, and mentally disabled individuals. The discreet and user-friendly nature of ODFs makes them a desirable alternative to conventional pills. The technology also presents opportunities for pharmaceutical companies to extend the patent life of existing medications and expand into new markets. While prescription ODFs are currently limited, several companies are actively developing FDOF technologies and collaborating with pharmaceutical companies to introduce these innovative products. The US FDA has established regulatory pathways for ODFs, indicating a promising future for wider adoption. The global OTF market has grown quickly, and forecasts suggest that it will continue to rise in the years to come. Increased patient compliance, the rise in chronic illness, and the need for more easily accessible over-the-counter drugs are some of the causes driving this trend.

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