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Mouth- Soluble Innovations: The Rise of Oral Dispersible Films in Modern Pharmacotherapy

Anju Bala[1], Inderjeet Verma[*2], Chander Parkash Dora[3]

[1]Department of Pharmacy, Maharishi Markandeshwar Deemed to be University Mullana, Ambala, Haryana.
[2]Department of Pharmacy, Maharishi Markandeshwar Deemed to be University Mullana, Ambala, Haryana.
[3]Chitkara College of Pharmacy, Chitkara University, Punjab, 140401

[*]**Corresponding Author: Dr. Inderjeet Verma**, Professor & HOD (Pharm.D), Department of Pharmacy Practice, M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala-133207, Haryana, India
Email Id: indupup@gmail.com

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ABSTRACT

Oral thin film is a drug delivery platform that has been demonstrated to be a method of administration that is acceptable to all age groups. The genesis of oral strip formulation began with the necessity to develop a dosage form that could be easily administered to patients suffering from dysphagia. Orally dispersible films are mainly preferred for elderly, pediatric, psychiatric, paralyzed, and mentally disordered patients. They are polymeric matrices that provide a controlled drug release to target sensitive spots, which is impossible to do with pills or liquid formulations. An oral thin film is a flexible, ultra-thin film containing an active substance that dissolves or disintegrates in the saliva at an incredibly fast rate, in a matter of seconds, without the use of water or chewing. The development of oral thin film products started with nonmedicinal products. Pfizer's first non-medicinal product was Listerine® PocketPacks™ strips, which were used as a mouth freshener. Film-forming polymers, organoleptic compounds, plasticizers, saliva-stimulating agents, thickeners, and stabilizers are utilized in the formulation of oral thin films. The surface area of fast-dissolving films typically ranges from 5 to 20 cm^2, and the drug is inserted in matrix form using a hydrophilic polymer. Since high-dose medications are challenging to combine into thin films and the film only comprises 5–30% w/w of the drug, low-dose pharmaceuticals were used. Solvent casting methods are mainly used for the manufacturing of oral thin film. Concepts and evolution, over-the-counter and prescription products, some patent technology, and previous work done by different researchers on oral thin film are discussed in this review. Finally, the review concludes by giving an overview of the ODF of herbal extract, patent, and clinical trials on the development of oral thin film.

Keywords: *Oral dispersible film (ODF), Concept and Evolution, Solvent Casting Method, 3D Printing Technology, Herbal Extract Film, Patent and Clinical Trials.*

INTRODUCTION

For the past two decades, the world has witnessed the evolution of delivery platforms that have forever changed the way drugs are administered to the diseased. Oral thin film delivery is one such system that has proved to be an important milestone in achieving compliance among different people. Oral thin film is a drug delivery platform that has shown to be one of the administration methods that has found acceptability among all age groups. The genesis of oral strip formulation started with the need to find a dosage form that could be easily administered to patients with dysphagia. The difficulty in swallowing dosage forms for underlying disease (Parkinson's)/old age presents a unique challenge of achieving optimal therapeutic outcomes, as missing doses can have a catastrophic effect on health. Another group of patients that has benefited from oral films is the pediatric age group [1]. Under the WHO initiative "Make Medicine Child Size", there has been a focus on formulating oral dispersible formulations, which have superior acceptability due to inherent swallowability and palatability, choking and vomiting [2]. When compared to liquid dose forms, oral films are less prone to dosing errors and parents' understandings of labeled instructions for dose administration [3]. Oral films can achieve different functionalities based on their design and excipients being used. So, oral films can achieve rapid onset of action, delivery through a specific area of the oral cavity through the adhesive properties of used polymers, adherence to a specific region of the oral cavity to mucosa (mucoadhesive) and rapid sublingual and buccal delivery. Other names of thin films appear as oral dispersible film, mucoadhesive film, oral soluble films, oral strips, oral thin films, wafers, buccal films, transmucosal film, and ophthalmic films [4]. Ideal thin films have to show alluring highlights like adequate drug loading capacity, quick disintegration rate or long duration at the point of administration, and stable formulation. They should also be non-toxic, biocompatible, and biodegradable. However, they were administered generally via buccal, ophthalmic, cutaneous, and sublingual routes [5]. Oral fast-dissolving films are polymeric matrices that provide a controlled drug release to target sensitive spots, which is impossible to do with pills or liquid formulations. A huge variety of drugs like neuroleptics, cardiovascular tablets, analgesics, antihistamines, antiasthmatics and medicines for erectile dysfunction are formulated in dispersible film [6].

From an industrial point of view, the market potential of oral films is important to ensure their future growth. Catalyst technology in 2007 reported the marketplace of oral thin film products. Oral dispersible film products are expected to be worth $500 million by 2010 and $2 billion by 2020. According to the Market Research report from 2018 to 2023, the global market for oral thin films is expected to grow at a 10.50% compound annual growth rate [7]. Currently, North America is the largest manufacturer of oral dispersible films and has launched more than 80 oral thin film brands since 2003. Major key players within the manufacturing of oral thin film include Pfizer, ZIM Laboratories Limited, Inc., Novartis AG, Indivior plc, MonoSol Rx, Sumitomo Dainippon Pharma Co., Ltd., Intel Genx Corp., Wolters Kluwer, Solvay and, Allergan plc. Around 38% of the products are supported by Labtec's rapid film technology and MonoSol's pharm film technology. Indian investors are looking at oral thin film as a superb opportunity for business. Bigger manufacturers like Cipla, Mankind, FFT Medicals, Cynapsus Therapeutics, and Dr. Reddy's laboratory are also emerging key player in oral thin film. New Indian companies such as Zim Laboratories Nagpur, Aavishkar Oral Strips Pvt. Ltd and NU Therapeutics Hyderabad have been extensively concentrating on this technology [8, 9]. Oral thin film is a flexible, ultra-thin film that contains an active substance that dissolves or disintegrates in the saliva at an incredibly fast rate, in a matter of seconds, without the use of water or chewing. Table 1 illustrates additional official definitions of thin films. The purpose of these polymeric films is to provide healing moieties through gastrointestinal absorption or regional or systemic dispersion within the oral cavity. Oral thin film was introduced to the market with appropriate product instructions, such as "do not swallow" or do not chew [10]. Oral thin films have been developed on the basis of transdermal patch technologies. These are composed on a large surface area of sheets and subsequently cut to the desired size and shape (Fig.1) [14].

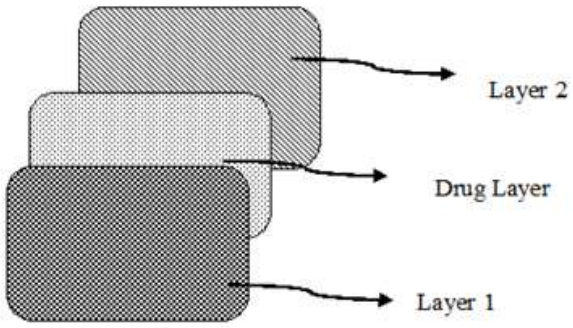

Fig.1. Schematic representation of oral dispersible film

TABLE-1
DEFINITION(S) OF ORAL DISPERSIBLE FILM

Name	Terminology used	Definition	Ref
United states pharmacopoeia	Oral thin film	Oral thin films are one or more layer of drugs with or without active pharmaceutical ingredients that are placed in oral cavity of mouth.	11
European pharmacopoeia	Oro-dispersible film	They are single or multilayered sheets of ingredients which is placed in mouth and disperse rapidly.	12
CDISC (Clinical data interchange standards consortium)	Soluble film dosage form	A thin sheet or covering of coating solution, when comes in contact with liquid or saliva is being dissolved.	13

1.1. General features of oral dispersible film

These possess several distinctive attributes that distinguish them from other oral dosage forms. Oral dispersible films are primarily preferred for patients with dysphagia, paralysis, mental disorders, psychiatric patients, and the elderly. These are lighter, easier to handle, and do not require a specially trained person. There is no need to drink water to swallow or chew, fast disintegration or dissolution, rapid onset of action, improved the bioavailability, and also enhanced stability of products. Oral dispersible films are available in a variety of sizes and shapes, and they have accurate dosing, which reduces GIT irritation **[15]. Figure 2** illustrates general features of oral dispersible film.

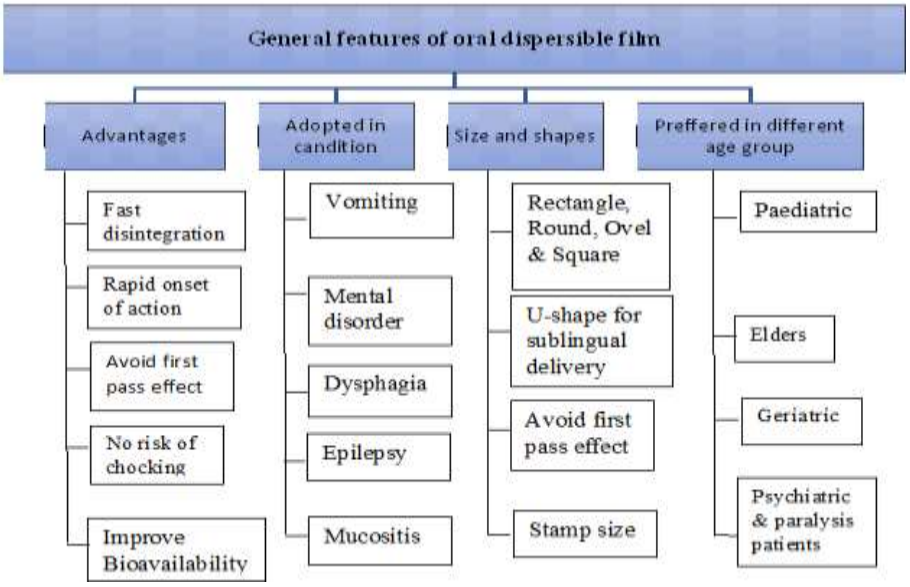

Fig.2. General features of oral dispersible film.

Release mechanism

In order to release the medicine for oral mucosal absorption, an open oral dispersible film is first deposited on the tongue of the patient or other mucosal tissues. Dispersible film is quickly moistened by saliva, disintegrates quickly, and dissolves. Because it dissolves in the mouth in under a minute without chewing or the use of water for delivery, it increases the efficacy of API dissolved. They are intended specifically for medications with substantial first-pass metabolism, low doses, and poor oral bioavailability **[16**]. When compared to a tablet, thin film has a bigger surface area and thinner film, which results in a faster release action. Release mechanism of oral thin film shown in fig.3. The acceptance of oral dispersible films depends upon patient compliance and pharmacotherapy of film. Therefore, to prove these aspects, researcher carried out surveys, and trials on oral films. In one study, Klingmann et al. performed a randomized controlled test on neonates and infants to find out the overall performance of film formulation compared to syrup formulation. The result of the study showed that oral dispersible films are a new, novel, safe, and better alternative than oral liquid formulations **[17]**. Another researcher, Orlu et al., accomplished a survey in infants and children from age 6 months to 5 years and reported a process or technique to accept the oral dispersible film as a dosage form. Findings of the study revealed a favorable reaction and demonstrated patient acceptance of the oral thin film as a dose form in children **[18].**

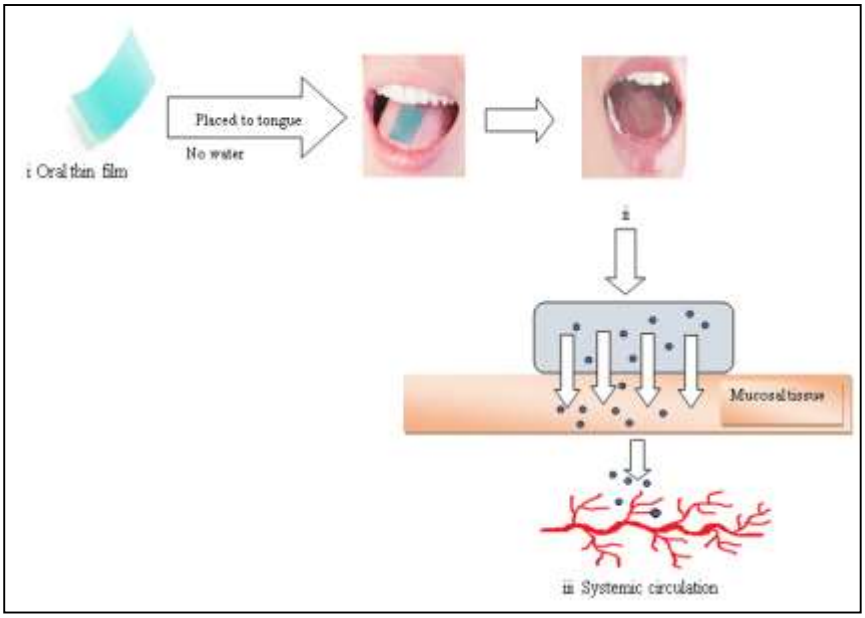

Fig.3. Release mechanism of oral dispersible film (i) Placed on tongue without aid of water & mastication (ii) Disintegrate & Dissolution (iii) Reaches to systemic circulation through mucosal tissue permeation.

In the present review paper, the first section described an overview of oral dispersible film. The second section deals with concept, evolution of oral dispersible film as a product and different technologies employed to manufacture thin films. Also focus on the formulation, characterization, marketed products of thin film, clinical trials, patents, current trends, and its future scope worldwide as well as in India.

2. Evolution and development of oral dispersible film

2.1. Oral dispersible film products

Dr. L.L. Frederick Deadman first proposed the idea of oral thin films in the early 1960s, and they were slowly developed until the end of the 1970s. As a result, they only existed as a concept until 2001 **[19]**. The development of oral thin film products started with nonmedicinal products. Pfizer's first nonmedicinal product was Listerine® Pocket Packs™ strips, which were used as a mouth freshener. After breath fresheners, the introduction of over-the-counter (OTC) and nutraceutical film formulations was launched on the market **[20].** The concept and evolution of oral thin films from nonmedicinal products to over-the-counter prescription products is shown in figure 4. The first medicated oral thin film, Chloraseptic comfort strips, was introduced by Prestige Brands and contains benzocaine and menthol for sore throat pain treatment **[21].** Novartis, in 2004, introduced two oral thin films. One was Theraflu, a thin strip of dextromethorphan for cough suppression and the second was Triaminic® with Diphenylhydramine hydrochloride for cold and cough **[22].** In 2005, Pfizer again entered the market with new over-the-counter film products such as Sudafed PE with the drug phenylephrine for nasal decongestion **[23].**

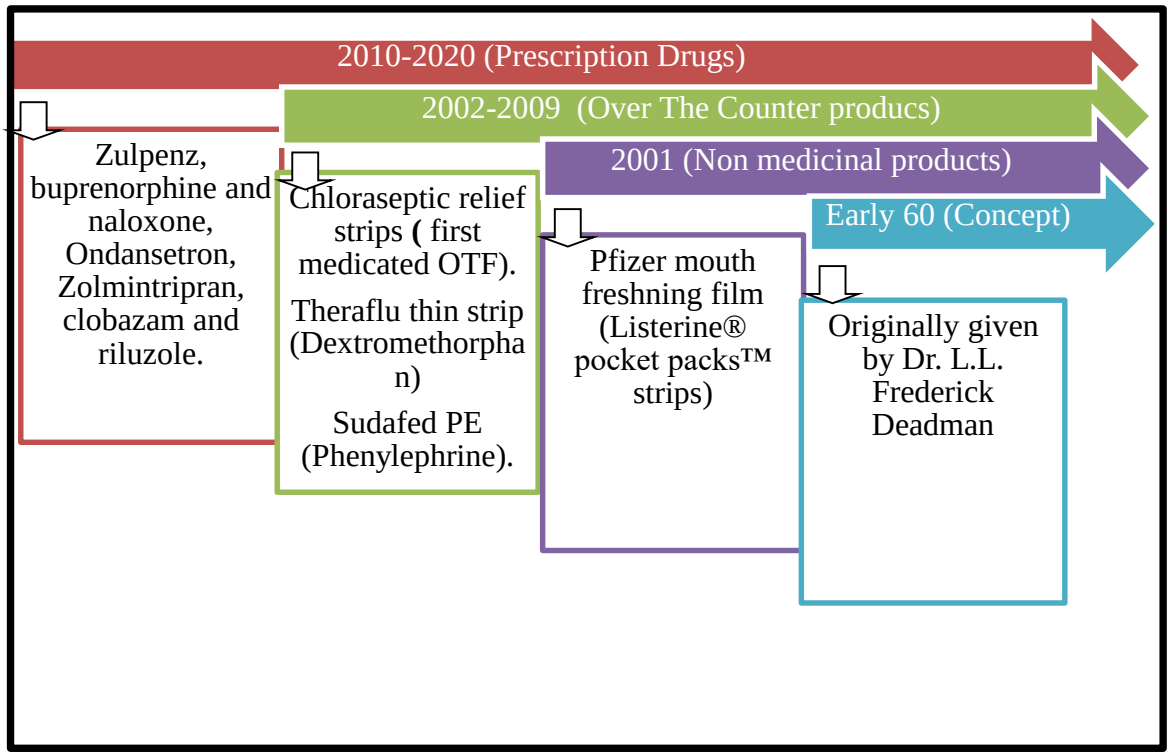

Fig.4. The concept and evolution of oral dispersible films from non-medicinal products to over the counter prescription products

InnoZen, Inc launched a suppress-cough strip with menthol. Labtec invented Donepezil film for Alzheimer's disease, and Seto film gives Ondansetron orally dissolving film, which is used as an anti-emetic. Wringley's invented Eclipse Flash Strips of mint. Oraj el of menthol was given by the Del for mouth ulcers. Solvay Pharmaceuticals launched Klonopin wafer of clonazepam for anxiety. Biofilm is also utilizing oral thin film products in nutraceutical and pharmaceutical areas as vitamins, energy boosters, aphrodisiacs, and appetite suppressors **[24]**. In 2006 and 2009, other over-the-counter pain relievers introduced by Novartis include simethicone and ketoprofen **[25]**. Thereafter, in 2010, the FDA approved the first prescription medicine of oral soluble disintegrating film, Zulpenz. The FDA then approved Reckitt Benckiser's buprenorphine and naloxone combination film for pain management based on Monosol's PharmFilm technology [26]. In addition, another major player, Labtec, launched ondansetron rapid film to relieve nausea in chemotherapy patients, and in 2013, Labtec released Zolmitriptan oral dispersible film for migraine treatment [27, 28]. In addition, Hexal launched the first oral films of risperidone for the treatment of schizophrenia [29]. GlaxoSmithKline launched nicotine oral dispersible films to reduce cigarette cravings in the 50s, and Velox introduced nutritional supplement-loaded strips [30]. Similarly, in treating colds and coughs of both adults and children, Forrester Pharma launched an oral thin film of the herbal extract Hedera helix [31]. ODFs

of sildenafil citrate in 2014 were introduced by Sandoz for erectile dysfunction [32]. Thereafter, in 2018, oral thin films of clobazam and riluzole were supplied to Aquestive Therapeutics for the treatment of epilepsy and orphan illnesses, respectively [33]. When compared to alternative dosage forms (tablets and suspensions), it is anticipated that the formulation's simplicity of administration will increase adherence and decrease dosage errors [34]. Table 2 lists some of the over-the-counter and prescription oral thin film products on the market.

TABLE-2

SOME MARKETED OVER THE COUNTER AND PRESCRIPTION PRODUCTS OF ORAL THIN FILM

Product Name	API	Manufacturer/Distributor
Listerine® Pocket Packs™	Cool mint	Pfizer
TheraFlu Thin Strips Triaminic® Neocitran®ThinGas-X	Dextromethorphan Diphenylhydramine Simethicone	Novarits
Chloraseptic	Benzocaine Menthol	Prestige
Sudafed	Phenylepinephrine	Pfizer
Suppress	Menthol	InnoZen, Inc
Donepezil film	Donepezil HCL	Labtec
Ondansetron ODF	Ondansetron	Setofilm
Klonopin Wafer	Clonazepam	Solvay Pharmaceuticals
Orajel	Menthol/pectin	Del
Zuplenz	Ondansetron	MonoSol Rx
Suboxone®	Buprenorphine/Naloxone	MonoSol Rx, Reckitt Benckiser
Donepezil Rapidfilm® Zolmitriptan Rapidfilm® OndansetronRapidFilm®	Donepezil Zolmitriptan Ondansetron	Labtec GmbH

2.2. Oral dispersible film technology

The following subsections employed some of the famous methods like solvent casting, extrusion, and rolling processes used by the researchers to fabricate oral thin films. Also include recent methodology and patent techniques used to design oral thin films.

2.2.1. Solvent Casting Method (SCM)

Compared to alternative processes, the solvent casting process is a commonly implemented for the preparation of oral dispersible films. In this method, firstly polymers that solubilize in aqueous solvents are dissolved in a suitable vehicle, and then other excipients, active pharmaceutical ingredients are either in water or an organic solvent using a high shear process. Finally, both mixtures are blended and agitated together to produce a viscous, homogeneous solution. The vacuum is used to liberate any trapped air, and the mixture is then carried to the casting station where it is cast into film on a release liner that has a thickness of 30-120 cm. After being cured in an oven, the cast film is then cut into the required shape. Schematic representation of the solvent casting method shown in figure. 5. In large-scale production, some special equipment, like rollers, is used to transfer the solution over to suitable base. Some special coating techniques, like reverse roll, knife-over-roll, gravure cylinder, slot-die, and Mayer rod coating, are used to coat the film. **[35, 36]**.

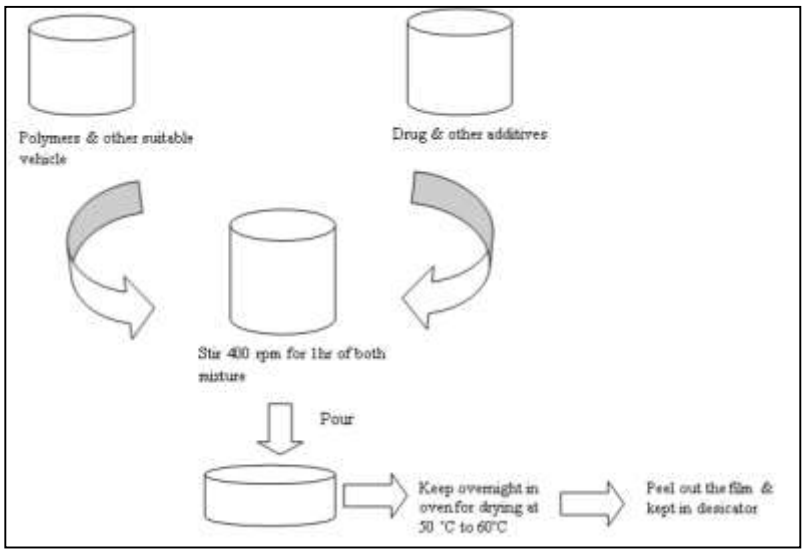

Fig.5. Solvent casting method

2.2.2 Extrusion Method

Hot melt extrusion

Solvent casting is replaced by the hot melt extrusion process, but this is often not suitable for thermolabile drugs because during this method all the exceptions are first melted on heat then cast into the film. The API and other materials are mixed, poured into the hopper, transported, mixed, and heated till the combination becomes molten and extruded out by the extruder. The film is cast from the molten mass that has resulted. The film is coated and then dried in a drying tunnel before being slit. Punched, pouched, sealed, and cut to the necessary sizes and shapes, the resulting films are punched, pouched, sealed, and cut to the desired sizes and shapes. In rhe pharmaceutical industry twin-screw extruder have been proven to be more beneficial because they provide homogenous and consistent mixing of multiple formulations, also leading to improved dissolution rates and bioavailability **[37]**. The processing temperature should be 650 -1150°C with the screw speed set at 15 rpm for 3-4 minutes. To generate a film with a thickness of 200 um, the temperature is adjusted to 650°C. This method required less time for the production, cost effective, better alternative for poorly soluble drugs, and had no need for the use of solvent or water **[2]**.

Solid Dispersion Extrusion:

Using procedures such as hot melt extrusion, one or more active medicinal substances are dispersed in a suitable carrier while in a solid state by using amorphous hydrophilic polymers. In this procedure, the drug is evacuated along with immiscible components, and solid dispersions are subsequently produced. The obtained solid dispersions are formed into suitable-sized thin films using dies **[38, 39]**.

2.2.3 Rolling method

In this method the solvent employed is mostly water and alcohol. This method involves rolling a polymer solution containing pharmaceuticals on a roller before drying the resulting films at the correct temperature. The created films are finally cut to the ideal size and shape **[40, 41]**.

2.3 Recent technologies used in the manufacturing of oral dispersible film

2.3.1 Electrospraying Technique

An innovative method for creating oral dispersible films called electrospraying involves spraying a solvent while being influenced by a strong electric field. The active pharmaceutical ingredients, polymer, and all other excipients are dissolved in a suitable solvent to create a transparent solution, which is then sprayed onto acceptable materials like glass, polyethylene film, Teflon sheets or, non-siliconized kraft paper. Polymer deposition is influenced by the energy of the polymer and substrate, the viscosity of the polymer/liquid mixture at deposition, and the size of the droplet or particle at deposition **[42]**.

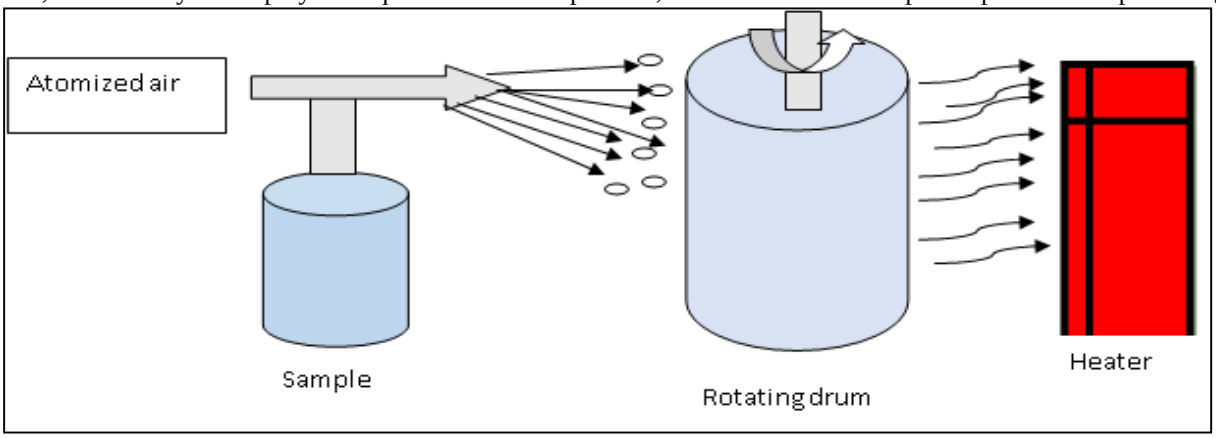

Fig.6. Electrospraying Technique

2.3.2 Electrospinning

One of the recent developments in the field of manufacturing polymeric films is electrospining. This technique provides an opportunity to prepare plasticizer-free films with requisite attributes. The electrospinning setup includes a needle, a fibre collecting substrate, a source of power supply, and an injection system. The solution is sprayed on the spinneret electrode to form a droplet that can interact with the electrostatic field. The droplet takes the shape of a cone, with a thin jet emerging from the top or tip of the cone. The fibers are then compressed by electrostatic forces between the two electrodes, which leads to the solvent evaporating and the formation of solid nanofibers. The resulting nonwoven web is removed as a sheet from the grounded collector **[43]**.

2.3.3 3D Printing Technology

Another film manufacturing technique that has gained popularity is 3D printing. It offers the advantage of being a single-step process with the opportunity to develop complex formulations. It has been used for preparing low dose tablets, polymeric films, transdermal patches, etc. There are different 3D printing methods for preparing oral films, namely extrusion-based 3D printing, vat photopolymerization, powder-based 3D printing, and inkjet 3D printing. The process of 3D printing starts with first designing the digital blueprint of the dosage form to be prepared. The prepared design is then converted to sterolithography file (STL). This is then fed to software that provides instructions to prepare the required product. Finally,

the printer facilitates the formulation into successive layers. This process continues till the final product is obtained. 3DP has the potential of replacing the conventional methods of manufacturing oral films because it can lend itself to processing a variety of different materials like lipids, polymers, surfactants, etc. This flexibility of 3D printing helps in achieving personalised dosage forms which can improve therapeutic outcomes **[44, 45]**. Many authors have formulated highly potent drugs using this technique mentioned in Table 3.

TABLE-3
POTENT DRUG MANUFACTURED BY 3D PRINTING TECHNOLOGY

Active ingredient	**Reference**
Proteins	Goodall S, Chew N, Chan K, Auriac D, Waters MJ
Salbutamol sulphate	Buanz ABM, Saunders MH, Basit AW, Gaisford S
loperamide and caffeine	Genina N, Fors D, Palo M, Peltonen J, Sandler N
Co-crystals	Buanz ABM, Telford R, Scowen IJ, Gaisford S
Rasagiline mesylate.	Genina N, Janßen EM, Breitenbach A, Breitkreutz J, Sandler N
Excipient-free salbutamol sulphate	Mueannoom W, Srisongphan A, Taylor KMG, Hauschild S, Gaisford S
Terbutaline sulphate	AG, Mueannoom W, Buanz ABM, Taylor KMG, Gaisford S

2.4 Patent technique

After over-the-counter to prescription products of oral thin film, patent technologies were also fabricated. Borges and colleagues presented patentable technologies. Table 4 provided the list of the patent technology employed to manufacture oral thin film by different manufacturers **[46]**. In order to create drug-loaded films, Dr. L.L. Frederick Deadman first introduced oral films in the early 1960s by coating, dipping, or spraying rice paper or gelatin films in a drug solution. Casting techniques employing film-forming polymers were also briefly explored in the early method [19]. All of the patented inventions are solely based on the solvent-casting process. Aquestive Therapeutics (formerly Monosol Rx/Kosmos Pharma) created PharmFilm technology to develop oral thin films, sublingual films, and buccal films. In this method, pre-mixed polymers (polyethylene oxide, hydroxypropyl methyl cellulose, etc.) are added to the feed tank first, followed by organic solvents and other additives. The mixture is added to the master feed tank and allowed to enter the mixers using the first set of metering pumps and control valves. The second set of metering pumps is used to supply the pan with the homogenous matrix created by the addition of the medication and other ingredients (flavoring agent) to the mixers **[47]**. Reckitt Benckiser's well-known brand Suboxone is made with PharmFilm technology. Following that, Labtec introduced RapidFilm and Thinsol technologies in 2006 and 2007. A casting solution of polyvinyl alcohol, starch, and polyethylene glycol is used by RapidFilm technology to produce single-or multilayer oral films. Similarly, Thinsol BioEnvelop used an enzymatically digested carboxymethyl cellulose casting solution with other suitable solvents. Versa Film technology was given by Intel Genx, which comprises a cellulose polymer, and the solution was cast on Kraft paper with a polyethylene coating and dried at 65°C. The SmartFilm technology was developed by Seoul Pharma to hide the bitter taste of the medication ingredient. Using this technique, Seoul Pharmaceuticals has successfully introduced or licensed medicines including sildenafil, tadalafil, and donepezil hydrochloride **[48]**. Soluleave technology provided a novel platform that will be fabricated to dissolve and releases the active ingredients quickly on contact with saliva. Cough/cold, pain therapeutic regions, gastrointestinal, and nutritional substance delivery are all possible applications for the technique **[24]**. XGel film technology was developed by Bio Progress Technology International, based in the UK, offering product innovation and manufacturing methods to the pharmaceutical industry. This method can encapsulate any type of oral dosage form and dissolve in cold or hot water. It potentially leads to the enhancement of the product stability and developed polymer films. XGel film technology is employed in a variety of applications, including ostomy pouches, cosmetics, sanitary products, and human healthcare equipment. The active component is precisely dosed within the prefabricated XGEL™ film body, reducing needless heat and moisture exposure and potentially improving product stability **[49]**. Another patented technology was BEMA (biodegradable mucoadhesive drug delivery system), which comprises a biodegradable polymer that adheres to the mucosal tissue within 5 sec and provides a uniform flow of drugs. The first marketed product was onsolisfenatyl buccal soluble film, launched in 2009 to relieve cancer pain in opioid-tolerant adults **[50]**. In 2005, the Hexal company launched Schmelzfilmen, or melting film products, by using cellulose derivatives like hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and ethyl cellulose. They developed four marketed products of films like olanzapine, sildenafil, donepezil, and risperidone **[51]**. Quicksol® technology is employed by SK Chemicals, which developed a wide range of drug substances but only two drug products are available in the market which are Mont Free oral thin film (montelukast) and Mvix-S film (mirodenafil) **[52]**. From the foregoing, it can be deduced that the solvent casting method is the most desired and industrially relevant approach. According to the previous findings, no new industrial platform technologies dealing specifically with the manufacture of ODFs were discovered after 2012.

TABLE- 4
LIST OF THE PATENT TECHNOLOGY

Sl.No	Company	Technology Name	Patent Number (s)
1	Aquestive Therapeutics	PharmFilm	US7357891
2	BioEnvelop (or Paladin Labs)	Thinsol	WO2009055923
3	LabtecGmbh	RapidFilm	WO2008040534 WO2009043588 WO2011124570
4	IntelGenx Technology Corp	VersaFilm	US20110136815
5	Hexal Pharmaceuticals	Schmelzfilmen	WO2007009801
6	SK Chemicals	Quicksol®	WO2013100564
7	Hexal Pharmaceuticals	Melting film	WO2007009800
8	Bio Delivery Sciences International	BEMA	WO2008011194
9	Seoul Pharma Co Ltd	SmartFilm	WO2013129889
10	Bio Progress	Soluleaves™	WO-2006114604

3 Formulation of oral dispersible films

All excipients used in the formulation of oral thin films must be generally considered as safe from a regulatory perspective and utilized in accordance with the Inactive Ingredients Limit (IIG limit). Mechanical qualities, flavor masking, rapid dissolving, tongue feel, and physical appearance are all considered during the formulation process. Film-forming polymers, organoleptic compounds, plasticizers, saliva-stimulating agents, thickeners, and stabilizers are utilized in the formulation of oral thin films. The surface area of fast-dissolving films typically ranges from 5 to 20 cm^2, and the drug is inserted in matrix form using a hydrophilic polymer. Excipients and active medicinal substances may be combined in amounts of up to 30 mg **[2]**. Since high-dose medications are challenging to combine into thin films and the film only comprises 5–30% w/w of the drug, low-dose pharmaceutical were used **[53]**. The ideal active components for pharmaceutical compounds are antiulcers, antitussives, antiepileptics, antiasthmatics, expectorants, antianginals, antihistaminics, antiemetics, anxiolytics, neuroleptics, analgesics, diuretics, antiallergics, cardiovascular agents, antiepileptics, sedatives, hypnotics, anti- Alzheimer's dysfunction agents, expectorants, anti-parkinson's agents and antibacterial agents for thin film **[54].** Excipients used in oral thin films are listed below by category, and all excipients used in the process must be chemically inert. On the other hand, the plasticizer was used in concentrations ranging from 0 to 20% weight/weight. Plasticizers are frequently utilized, and some examples include propylene glycol, glycerol, low-molecular-weight polyethylene glycols, polyethylene glycol 4000, citrate derivatives such as acetyl triethyl citrate, triethyl citrate, and tributyl citrate, castor oil, triacetin, malic acid, and sorbitol **[55].** It has been asserted that some polymers, including Kollicoat IR and polyethylene oxide, have a self-plasticizing effect, negating the need for an additional plasticizer in the film formulation. Pullulan and hydroxypropyl methylcellulose are two examples of hydrophilic polymers that are frequently used because they give the film quick disintegration, a pleasant mouth feel, and high mechanical energy **[56]**. The usual range for polymer concentrations is 5% w/w to 10% w/w; however 5% w/w is preferred. Citric acid, lactic acid, malic acid, tartaric acid, and ascorbic acid are used between 2 and 6% w/w of the oral thin film and are used either alone or when combined with other ingredients to increase salivation. Stabilizers like natural gums or cellulosic derivatives are used at a concentration of about 5% w/w. Organoleptic components are made up of different coloring agents like titanium dioxide or FD&C-approved colorants, which are not used in concentrations greater than 1% w/w, and sweetening agents such as maltose, glucose, fructose, xylose, or maltodextrins. Other flavoring ingredients like cinnamon oil, peppermint oil, cherry, raspberry, pineapple, etc. are employed singly or in combination at a concentration of around 10% weight to weight **[57].**

The following subsections of formulation provide oral thin films of active pharmaceutical ingredients, herbal extracts, probiotics, and vaccine.

3.1 Oral dispersible film of active drug substances

The rationale for drug selection is based on the drug's permeability and solubility. Drugs from BCS classes II and III are typically used to make oral thin films. The previous research work reported that the authors mainly used solvent casting process for the fabrication of oral dispersible film. Table 5 shown the list of drugs loaded as oral dispersible film. All these aspects are cleared from the discussion given below. Sanjay Kumar et al. in 2020 formulated mirtazapine oral dispersible film by the process of the solvent casting, and results of the study reported that the film disintegrated in less than 5 sec and prolonged the drug release **[58].** However, in 2020, Madihamushtaque et al. introduced an oral thin film of escitalopram by using hydrophilic polymer, and the film avoided first-pass metabolism which enhanced the convenience and pediatric patient

compliance **[59]**. Similarly, Latif et al. proposed oral thin films of alprazolam with excipients HPMC E5, PEG-400, HPMC E15, PEG-6000, aspartame, and citric acid monohydrate by solvent casting technique. The film showed high drug loading, optimum mechanical strength, and less disintegration time **[60]**. In 2019, another group of researchers, Rathore et al. published an oral thin film of zolmitriptan for migraine treatment. In comparison to current traditional dose forms, the film demonstrated extremely fast onset of action in severe conditions of migraine attacks **[61]**.
In 2018, Lakshmi P.K. et al. developed atomoxetine hydrochloride oral films employing a variety of polymers, including HPMC LV grades, guar gum, polyvinyl alcohol, sodium alginate, and super disintegrants such as SSG, CCS, CP, and KYRON 314. The Taguchi OA experimental model was used to analyzed the generated formulations from preliminary trials. The results show that the disintegration time and drug release rate are influenced by changing the type and amount of film polymer **[62]**. Ehtezazi T et al. in 2018 proposed fast dissolving multilayered film by the 3D printing technologies for masking the taste of drugs. At 60°C and 130°C, the formulations were made by mixing paracetamol or ibuprofen with polyethylene oxide and polyvinyl alcohol. For a taste-masking layer, another formulation was created by mixing polyethylene oxide and strawberry powder. Oral film made of polyethylene oxide printed at 165°C and polyvinyl alcohol printed at 190°C that dissolves quickly. According to the findings, 3D printing technology produces thin film mesh designs that shorten disintegration times **[63]**. However, in 2018, Patil D et al. employed solvent casting method to generate a fast-dissolveable Telmisartan film using excipients like polyvinyl pyrrolidone, propylene glycol, and polyethylene glycol. The study's major goal was to extend the dosage form's release time at the absorption site, resulting in improved absorption and bioavailability **[64]**.

Kadam V et al. and Bajpai s et al. developed a fast dissolving oral film of metoclopramide hydrochloride and amoxicillin composed of casein and sodium alginate**.** The results of the study concluded that the drugs formulated as film showed better patient compliance than solid dosage forms **[65, 66].** Sheenam Mansoori et al. (2017) used polymers such as maltodextrin, and hydroxypropyl methyl cellulose E3, E5, and E15 to create an oral thin film containing domperidone hydrochloride. Within 2 minutes, more than 95% of the drug formulation was released, indicating that hydroxy propyl methyl cellulose E5 resulted in faster drug release and disintegration time of less than 60 seconds **[67].** VD Prajapati et al. developed a pullulan-based fast-dissolving zolmitriptan film that was tuned using a factorial approach to improve the drug's poor oral bioavailability **[68].** Losartan potassium's oral dispersible film was created by Raghavendra Rao et al. in 2016, and the outcomes demonstrated that the oral thin film of losartan potassium had a fast onset of action, minimizing the first pass-effect and consequently enhancing the rate of absorption **[69**]. Martina Aduenimaa Bonsu et al., in 2016, used albizia and khaya gums as hydrophilic film formers to create oral fast-dissolving films containing diclofenac sodium for the treatment of osteoarthritis, and the film delayed the drug's release **[70]**. Similarly, Patil et al. in 2016 designed fast-dissolving strips of the drug metoprolol succinate and therefore concluded that this delivery system was more effective therapy than conventional tablets **[71].** Reddy et al. created an oral buccal film of zolmitriptan using cellulose derivatives, and they discovered that the ideal formulation had a disintegration time of 56 seconds and a drug release rate of 99.89 %**.** Pathan et al., used the solvent casting process to develop and analyze a promethazine hydrochloride film with various surfactants **[72, 73].**
In 2016, Karunakar et al. produced and compared studies of an oral, rapidly dissolving thin film of alendronate that was cast using different polymer amounts to have higher tensile strength and folding endurance **[74].** A lamivudine thin film was developed and tested for pediatric medicine by Ramya Teja et al., in 2015. Rapid drug solubility was discovered through oral thin films, preventing first-pass metabolism and enhancing patient compliance **[75]**.

A montelukast sodium oral film was created by Munda da et al. (2015) using Musa Paradisiaca powder as a special super disintegrant and hydroxy propyl methyl cellulose E15 LV as the film-forming agent. When the formulation was optimized using a 32 full factorial design, it was found that increasing the polymer concentration has negative effects on the disintegration time and dug release, while increasing the concentration of Musa Paradisiacal powder has positive effects on the drug release and onset of action, which may improve oral bioavailability **[76]**. Gautam et al. used the solvent casting technique method to create promethazine theoclate orally rapid dissolving thin film for the treatment and control of nausea and vomiting in 2015 **[77]**. For pain management, K Senthil Kumar, et al. created a mouth-dissolving film of etoricoxib. Etoricoxib's solubility and taste were improved by combining it with beta-cyclodextrin in a drug inclusion complex **[78]**. In 2014, Prabhu et al. used a solvent casting approach to create an oral thin film of lisinopril utilizing a variety of various polymers, including HPMC E5 LV, HPMC 4KM, and, HPMC E 3, as well as polyethylene glycol as a plasticizer **[79].**

Ramani Gade et al. created an oral thin film of pravastatin sodium utilizing natural mucilage from ocimumbacilicum seeds together with additional components such as polyethylene glycol 400, glycerine, aspartame, eugenol, xylitol, sorbitol, and mannitol in 2014. A formulation using polyvinyl alcohol and mucilage powder of ocimumbacilum in the ratio of (1.5 percent: 0.5 percent) was found to be acceptable for rapid dissolving oral films. According to the findings, formulations have a shorter disintegration time and a faster drug release **[80]**. In 2013, Farhana sultana et al. used excipients like hydroxy propyl methyl cellulose (15 cps), Kollicoat IR and sodium alginate to create rapid dissolving thin films of anhydrous Caffeine. In vitro tests revealed that the polymer Kollicoat IR white formulation was more porous and dissolved in 12 seconds **[81]**.

TABLE- 5
LIST OF PREVIOUS DRUGS FORMULATED AS ORAL THIN FILM

Drug	Excipient	Outcome	Ref
Mirtazapine	HPMC E6, PG, CMC, crosscarmellose, sodium alginate, aspartame,citric acid	Bypassing first pass metabolism	58
Escitalopram	HPMC, PEG 400, sodium dodecyl sulfate, cross carmellose, vanillin, citric acid, methanol	Avoide first pass metabolism and enhances life cycle of the drug	59
Alprazolam	HPMC E5, HPMC E15, PEG- 400, PEG-6000, Aspartame. Citric Acid, Monohydrate	PEG-6000 and PEG-400 were analysed separately or in combination at variousconcentrations.	60
Zolmitriptan	PVA, Maltodextrin, HPMC E50, PEG	HPMC E50 showed better acceptance	61
Atomoxetine hydrochloride	HPMC LV, HPMC LV 50, Guar Gum, PVA	Optimized formulations found to be stable for 1 month.	62
Paracetamol, ibuprofen	Polyethylene oxide	3 D printing reduce the film production time, reduce disintegration time and also masking the taste.	63
Telmisaratan	Poly vinyl pyrrolidone, PG 400, PEG	Increase the release time of drug, enhance bioavailability and absorption.	64
Metoclopramie HCL	HPMC E5, K4M, E15, K15 and PEG-400	Avoid first pass metabolism	65
Amoxicillin	Casein and Sodium Alginate	Fast release of amoxicillin via oral mucosa route.	66
Domperid one hcl	Maltodextrin, HPMC E15, HPMC E5, and HPMC E3.	The most effective treatment for ADHD and narcolepsy.	67
Zolmitript an	Peg 400, Sucralose, Pullulan	Pullulan successfully utilized at lab scale	68
Losartan Potassium	HPMC, sodium starch glycolate, Crosscarmellose Sodium, Crospovidone	Increase the absorption by reducing the first passeffect.	69
Diclofinac Sodium	HPMC E15, Aspartame, Pineapple flavor, Tween 80, Titanium dioxide and Glycerol	Gums from albizia and khaya were utilised to create diclofenac sodium thin film.	70
Metoprolol succinate.	HPMC, PVA	Enhanced dissolution rate of drug & better patient compliance.	71
Zolmitriptan.	HPMC-E5, HPMC-E15, HPMC-E50 Citric acid, PEG, Sodium saccharine	Enhance poor oral bioavailabilityand avoidpresystemic metabolism of drug.	72

Promethazine hydrochloride	HPMC-E15, PEG 400, SLS, MCC, Sucrose, Strawberry	Enhanced poor bioavailability of drugs.	73
Alendronate.	Sodium starch glycolate, HPMC, Vanilline, Guar gum, Sodium saccharide.	Increase tensile strength and folding endurance.	74
Lamivudine	HPMC E15, HPMC, Xanthan gum, guar gum, Aspartame, PG	The best results were obtained using a combination of sodium alginate and HPMC 3cps.	75
Montelukast sodium.	HPMC E15LV, Musa paradisiaca fruit powder	Musa paradise powder showed fast release of drug and rapid onset of action than HPMC E15LV	76
Promethazine theclate	PVA, HPMC, HPMC K15,HPMCE50, PG, Cross povidone, Citric Acid, Tween80, Aspartame	Better than conventional treatment for nausea &vomiting.	77
Etoricoxib	Betacyclodextrin, Sucralose, Methanol, Acetonitrile	Inclusion complex enhanced solubility &masking the bitter taste of drug.	78
Lisinopril	HPMC E5 LV, HPMC 4KM, HPMC E 3 PEG	For the management of Hypertension and cardiac disease.	79
Pravastatin Sodium	OcimumBacilicum seeds, PVA, PEG 400, glycerine, aspartame, eugenol, xylitol, sorbitol, mannitol.	PVA and ocimumbacilum mucilage powder suitable for better film	80

PG: propylene Glycol, PEG: Polyethylene Glycol, HPMC: Hydroxypropylmethyl cellulose, PVA: Polyvinyl alcohol, SLS: Sodium lauryl sulfate, MCC: Micro crystalline cellulose

According to the previous study, the medications used in the formulation are very small molecules that have undergone thorough reduction before being loaded into thin film formulation. Oral dispersible films (ODFs) overcome the limitations of oral drug delivery systems, but still they have some limitations like poor solubility, permeation, and drug elimination, etc. Poorly-water soluble drugs are not suitable for oral dispersible film because they have poor oral mucosal drug absorption. Taste masking with bitter drugs is also another major challenge in oral thin films. To resolve all these aspects, a new medicine delivery mechanism is required. Table 6 provided the list of previous novel drug delivery approaches used to formulate drugs as oral thin films. The discussion of all the aspects of Using d-tocopheryl polyethylene glycol succinate (TPGS-1000) and poloxamer-188, Islam N et al. developed orodispersible sublingual films of mixed micelles. To increase ebastine oral bioavailability, micelles were made using a thin film hydration technique. **[81]**. Similarly, Anna Karagianni et al. prepared itraconazole nanocrystals by the wet pearl milling method and composed them into a polymeric film to enhance the solubility of the drug **[82]**. Yet in another study, Pankaj A. Jadhav et al. created a flurbiprofen oral thin film loaded with polymeric nanosuspension and prepared the film using the solvent casting process. According to the findings, thin films have the capacity to stabilize nanosuspensions and improve medication release **[83]**. Wai Houng Chou et al. on the other hand, developed a unique mucoadhesive film of lipid micelles for buccal administration of biologicals and drugs that are poorly soluble in water in the year 2020. A heated emulsification approach was used to create lipid core micelles. This approach produces micelles that are tiny and spherical in shape, contain negatively charged carriers, and have a high entrapment efficiency, and insulin released more drug than rhodamine lipid core micelles in an in vitro investigation **[84]**. Dikshita Ullas Chavan et al. developed felodipine nanoparticle strips that dissolve quickly for managing angina and excessive blood pressure. The nanosuspension formulation was prepared using a solvent-antisolvent precipitation process and analyzed using standard software 23 factorial design expert® 12. The final optimized film compositions offer excellent

physical and mechanical qualities, as well as quick medicine delivery and long shelf life **[85]**. Another study used the nanoprecipitation approach to create orally quick- dissolving films made up of buspirone hydrochloride nanoparticles. According to the findings, formulation improved medication bioavailability and provided long-term drug release **[86]**. By using a solvent casting approach, Seema Pattewar et al. were able to create and characterize a self-microemulsifying mouth-dissolving film of piroxicam. Design-Expert® software version 10 was used to optimize the film. Self-microemulsifying film's in vitro drug release was 98.04±0.016% in 5 min, and it provided immediate absorption of piroxicam **[87]**. In another study Bhavesh D. Kevadiya et al**.** used the wet media milling process for the manufacturing of fenofibrate nanocrystals. The results of the study concluded that the approach of drug nanocrystals and then incorporation into film has a significant effect on bioavailability enhancement of the drug **[88]**. Similarly, utilizing an ionic gelation process and sodium tripolyphosphate as a crosslinker, Nusaiba K. Al-Nemraw et al. created and investigated chitosan nanoparticles of insulin loaded in buccal films. The release of insulin from the nanoparticles was then investigated when the nanoparticles were mixed with buccal films. Finally, the in vivo performance of insulin-loaded chitosan nanoparticles was examined, and the results were contrasted with insulin that is currently on the market. The created films were found to significantly reduce glucose levels in diabetic rats [89]. Chitosan microparticle-containing buccal films were made by Batista P et al. for the administration of bioactive peptides. The films were created using the solvent casting technique, while the microparticles were created using the ionic gelation method. The produced oral films were more flexible, had better elasticity, were easier to transport, and disintegrated quickly **[90]**. Using the solvent casting approach, Soroushnai A et al. published a nanosuspension-loaded fast- dissolving, dispersible film of anti-epileptic medication in 2018. Nanosuspensions were created using an ultrasonic technique and then mixed with other substances such as glycerol and cellulose nanofiber in a hydroxypropyl methyl cellulose/pullulan polymeric matrix. According to the findings, nanosuspension in buccal films improves orotransmucosal absorption and drug solubility **[91]**. Another group of researchers, Chen Liu et al., developed and tested an oral thin film of lutein nanocrystals to improve drug bioavailability. Anti-solvent precipitation was used to make nanocrystals, which were subsequently included in the films via the solvent casting procedure. Box-Behnken Design performed formulation optimization. The size of the particle of nanocrystal-formed film is 377.9 nm, which gives faster drug release and greater folding endurance than the usual oral quick-dissolving film of raw lutein. The findings suggest that using a drug-loaded nanocrystals film improves the bioavailability of the poorly soluble medication lutein **[92]**. Ankita D. Chonkar and colleagues created a film of lercanidipine hydrochloride nanoparticles in a polymeric semicrystalline matrix to improve the drug's solubility and ex vivo penetration. Ex vivo drug permeation of the film indicated quick dissolving and increased permeability of nanoparticles in an in vitro dissolution test. The study's findings revealed that nanoparticles in polymeric films boost bioavailability and orotransmucosal absorption **[93]**. To increase the absorption and prolong the impact of metoprolol tartrate, Ayat Allam et al. created sublingual quick-dissolving niosomal films **[94]**. AI-Nemrawi Nusaiba K., et al in 2015, formulated and characterized acetaminophen nanoparticles by the emulsion-solvent evaporation method. All of the film and nanoparticle properties were based on the excipients that were employed to make the films. By increasing the amount of polyvinyl alcohol and hydroxy propyl methyl cellulose the size of the nanoparticles also increased. Drug release parameters indicate that the nanoparticles were released from the films in less than one minute, and the nanoparticles showed a sustained drug release for up to 12 h **[95]**. Another study sought to develop a sublingual film incorporating nanoparticles as a treatment for nausea and vomiting brought on by chemotherapy. Depending on the amount of the polymer hydroxypropyl methylcellulose E 5, the drug's release was determined. A high-speed homogenizer was used to make the nanosuspension, and the research found that the amount of the polymer hydroxypropyl methyl cellulose E 5 affected how much medication was released. The impact of various polymer hydroxy propyl methyl cellulose E-5 and propylene glycol concentrations on formulation disintegration time, tensile strength, and percent in vitro drug release was examined using a 32 factorial design. According to the findings, the rate of dissolution increased in the film containing drug nanoparticles **[96]**. Buccal films of mixed micelles of phospholipid and bile salts were produced and assessed as a successful transporter for cucurbitacin B delivery for cancer treatment by Qingyuan Lv et al. When compared to regular carboxymethyl chitosan films and oral marketed tablets, Cu B nanoscale carboxymethyl chitosan films exhibit a longer-lasting release (Hulusupian). According to the findings, mucoadhesive buccal film could be a safe alternative for delivering Cu B with better patient compliance and absorption **[97]**. Lou H et al, prepared oral disintegrating film of chlorpheniramine maleate microparticles for pediatrics use. The results of taste veiling test demonstrated that microparticles reduce bitterness of drug significantly. Additionally, chlorpheniramine maleate was added to eudragit microparticles by spray drying a water-in-oil emulsion **[98]**. Elaheh Mortazavian et al, also reported a chitosan buccal film containing insulin nanoparticles and a thiolated chitosan derivative. Ex-vivo tests were performed on rabbit buccal mucosa that had been removed. The final optimized insulin nanoparticle formulation with acceptable physicochemical properties. Insulin nanoparticles have the highest solubility in aqueous solutions, according to their in vitro release rate **[99]**. In 2013, Shen BD et al. developed and analyzed an orodispersible Herpetrione nanoparticle-containing film. High-pressure homogenization was used to make nanosuspensions, which were then combined into an oral dispersible film containing drug nanoparticles.To increase the bioavailability of ineffective water-soluble medications nanosuspensions containing drugs are suspended into a thin film **[100]**. Priyanka Rana et colleagues. on the other hand, developed and tested mucoadhesive buccal films containing carvedilol nanosuspension, which was made using a ultrasonication techniques of precipitation with different polymer amount. Layer of drug gel was fixed between a backing and mucoadhesive layer, and

an optimized nanosuspension formulation to make triple layer buccal films. According to the findings, this delivery mechanism is an excellent way to administer medications with a high first-pass metabolism **[101]**.M. Zhang et al. developed and studied a self-microemulsifying vitamin D3 oral thin film for newborns. The film formulation was optimised using orthogonal experimental design, and the microemulsion was created using the water titration method. The resulting oral thin film of vitamin D3 had a thickness of 166.7 3.30 m, a rigidity of 38.45 3.72 MPa, a prolongation of 23.38 4.23%, and a folding endurance of more than 200 times. The film decomposed in about 18 seconds **[102]**. Concetta Giovino et al. developed and characterised chitosan films encapsulated with PEG-b-PLA nanoparticles loaded with peptides. These films were made using a solvent casting procedure by varying the concentration of insulin ((1, 3, and 5 mg of nanoparticles per film).The film with 3 mg of nanoparticles per film was shown more mucoadhesion **[103]**. Another study used an emulsion-solvent evaporation process to create and assess buccal films of selegiline-loaded nanospheres. Experiments done in vitro and in vivo showed that the generated buccal film has the potential to increase selegiline absorption by extending retention duration, providing regulated release, and enhancing bioavailability **[104]**.

TABLE- 6

NOVEL DRUG DELIVERY SYSTEM USED IN ORAL THIN FILM

Carrier	**Drug**	**Excipient**	**Outcome**	**Ref**
Micelles	Ebastine	α-tocopheryl, PEG, Succinate,Poloxamer-188	Enhance bioavailability of ebastine	81
Nanocrystal	Itraconazole	HPMC, Poloxamer 407, Glycerol	Improved solubility	82
Nanosuspension	Flurbiprofen	Poloxamer188, HPMCE15, Glycerol	Enhance dissolution rate of flurbiprofen	83
Micelles	Insulin, Rhodamine 123	HPMC K100, EC Tween 20, Span 80, Trifluroacetic acid	Micelles enhanced permeation of drug	84
Nanosuspension	Felodipine	PVP K30, PVA, HPMC (E5, E15) LV, PEG 400.	Nanoparticles improve low solubility and bioavailability of drug	85
Nanoparticles	Buspirone hydrochloride	HPMC E15, Poloxamer 188, Maltodextrin, PVA, Sodium alginate, PG, PEG-400	Enhance bioavailability of drug with poor water solubility	86
Microemulsion	**Piroxicam**	Aspartame, PEG-400, polystardonecrospovidone, HPC, Cremophor-EL Transcutol P, HPMC E15, Magnesiumaluminometa silicate	Overcome water-solubility issues of drug	87
Nanocrystals	Fenofibrate	HPMC, Glycerine, SDS	Enhanced oral bioavailabilty	88
Nanoparticles	Insulin	Sodium tripolyphophate, Chitosan	Insulin chitosan nanoparticles film decrease glucose level rapidly than commercially available insulin	89
Microparticles	Peptide	Chitosan, TPP, α- amylase, Bovine, Pepsin, Citric acid, d-sorbitol trifluoroacetic acid, Pancreatin, Pot. phosphate	Microparticle enhanced the stability of formulation.	90

Nanosuspension	Midazolam	HPMC, Glycerol, Cellulose,	Controlled severe neuropathic attacks in children.	91
Nanocrystal	Lutein	PEG 400, HPMC, Cremophor EL	Enhanced bioavailability of poor soluble drugs lutein.	92
Nanoparticles	Lercanidipine	PEG 400 and TPGS 1000	Nanoparticles increase dissolution and permeability.	93
Niosomes	Metoprolol tartrate	HPMC E15 MC, microcrystalline cellulose, PEG400, Cholesterol, span 60, saccharine	Extend the duration of the drug's therapeutic action and increase bioavailability.	**94**
Nanoparticles	Acetaminophen	PEG, HPMC, poly(lactide-co glycolideacid), PVA, aspartame	Nanoparticles released less than 1 minute from film and provide sustained drug release over 12 h.	95
Nanoparticles	Domperidone HCL	HPMEC, Propylene glycol, aspartame, carbopol 934P	Nanoparticles increase dissolution rate	96
Micelles	Cucurbitacin B	carboxymethyl chitosan, Glycerol, phospholipid-bile salt	Buccal film containing micelles showed best patient compliance and greater absorption.	97
Microparticles	Chlorpheniramine Maleate	Eudragit	Oral film of chlorpheniramine maleate microparticles have a great potential to mask the taste of drug for pediatric uses.	98
Nanoparticles	Insulin	Chitosan, Sodium tripolyphophateglycerol,	Insulinchitosan nanoparticles film was a great enhancer for delivery of insulin at buccal site.	99
Nanosuspension	Herpetrion	HPMC,HPC,Microcrystaline cellulose, PEG 400	Enhance bioavailability of poor water soluble drug.	100
Nanosuspension	Carvedilol	PVA, Potassium dihydrogen orthophosphate, EC PVP-K90, HPMC 15, PEG 400, SA, Carbopol 934P, Tween 80, KBr	The use of nanosuspension in mucoadhesive films showed higher drug release.	101
Microemulsion	vitamin D3	MC, lauric acid, tween80, N-hexane, acetonitrile	Improves the dissolution rate, bioavailability, good stability	102
Nanoparticles	Insulin	PLA, glycerol, Chitosan, PEG, PVP, PVA, trehalose, trifluoroacetic acid.	Insulin nanoparticles take less time to reduce glucose level than tablet.	103
Nanospheres	Selegiline	Poly(lactide-co-glycolide), HPMC	Best approach to overcomeparkinson'sdisease .	104

3.2 oral dispersible film of Herbal extract

A large study discovered that herbal drugs or extracts have a wide range of medicinal properties such as antibacterial, anti-inflammatory, antifungal, antispasmodic, anticancer, anti-HIV, antioxidant, anti-amoebic, antifertility and anti-diabetic etc. These are act slowly when administered orally and undergoes first pass metabolism. Therefore, to overcome the oral

limitations of herbal dosage form they are formulated into thin film. Sultana and colleagues used the solvent casting process to create a quick dissolving buccal film containing curcumin with excipients polyethylene glycol (PEG4000), polyvinyl pyrrolidone (PVP k30), Lycoat RS720 polymer and plasticizer glycerine. The purpose behind this study was to give a faster onset of action, improve bioavailability, and improve patient acceptance **[105]**. Similarly, Anwar S Daud et al used a solvent casting method to create oral films of Zingiber officinale by using hydroxy propyl methyl cellulose. Cough, anorexia, motion sickness, nausea, and vomiting are all treated with these films. Results of study showed that HPMC 5 cps is the stable and best film forming polymers **[106].** Another study on Cannabis Indian hemp captured all over the world and reported various patent and marketed dosage form. Cannabidiol (CBD) oil is one of the commercially accessible dose forms of cannabis and tetrahydrocannabinol (THC) oromucosal spray approved by FDA **[107, 108].** The US patent for dissolving films containing cannabis whole plant extract or cannabis oil with tetrahydrocannabinol alone or in conjunction with additional cannabinoids or cyclodextrin belongs to the renowned IntelGenx Corporation [109]. Currently, IntelGenx exported 75,000 CBD thin film strips to Heritage Cannabis Holdings Corporation using its unique VersaFilm technology [110]. Concept Matrix Solutions (CMS), a US-based company, has been awarded yet another cannabis patent for oral thin films containing either pure cannabis plant extract or cannabis plant extract combined with kava plant extract **[111,112].** Similarly Rapid dose therapeutics manufacturer develop an international patent on single layered oral film of Cannabinoids with other products like nicotine, melatonin, vitamin B12, iron, caffeine, curcumin and organic or inorganic therapeutic salts **[113].** Another company, F6 Pharma Inc, reported patent applications on oral thin film of CBD with excipients like butylated hydroxy toluene (BHT), chlorophyll and peppermint oil **[114].** Yunnan Pharmaceutical Research Institute developed oral thin film of analgesic and anti-inflammatory chemical constituent 'Bulleyaconitine and the film were prepared by forming the complex with polymer polyacrylic acid resin. The bitter taste of constituent mask by menthol **[115].** Another than complexing with polymer nanotized bio-active herbal extracts were also developed as oral thin films. Jittinan and colleagues developed fast-dissolving film of composed of nanoparticles of antibacterial mangosteen extract for the treatments of bad mouth odor. The films were manufactured by solvent casting method and nanooarticles contains film-forming polymer pullulan-alginate, mint oil and glycerol. Results of study concluded that film showed antibacterial effect against Streptococcus mutants, S. sanguis and Porphyromonasgingivalis (P. gingivalis**) [116].** Wrigley Jr. Company designed, a pullulan based edible film comprising of Magnolia bark extract for oral cleansing and breath freshening benefits. Film used oral cleansing agents with vitamins or minerals and reported that there is no need to carry any device like toothbrush or tongue cleaner during the travelling **[117].** From all the above, aspects it is apparent that research on herbal oral thin film is more advantageous and more research is warranted in this field.

4 Oral dispersible films characterization

Oral dispersible film characterization studies include morphology studies, drug – excipient compatibility studies, mechanical strength of the film, disintegration, dissolution and stability studies of film. Surface morphology of film such as color, homogenicity, transparency, flexibility, brittleness of thin films was determined by visual inspection or by using the instrument scanning electron microscope. Likewise, Differential scanning calorimetry was also used to test drug compatibility with other excipients **[24, 43].** Light emitting diode and dependent resistor are new technologies which correctly assess the beginning and end points of film disintegration. Another method of determination of disintegration of film is petri dish plate method. This method has major limitation of lack of determination starting and end point of disintegration of film. The stability of films depends upon moisture contents in films which is investigated by many procedures like Karl Fischer titrations. The acceptance limit of moisture content is 3 to 6% [118]. Apart from these parameters mechanical characterization of oral thin film also important to ensure its handling. The mechanical qualities of the ODF are also important to ensure that the end-user can handle it easily. The European Pharmacopoeia does not provide any recommendations or tests for determining the mechanical qualities of OTF, but it does mention that the maker must ensure that they are "mechanically strong enough to withstand handling without being destroyed." **[12].**On the basis of these aspects, researchers tested the film's thickness, tensile strength, percent elongation, tear resistance, and young modulus. The film's ideal tensile strength should be larger than 2 N/mm^2, its percent elongation to break should be greater than 10%, and its young's modulus should be less than $550N/nm^2$ **[118].** Table 7, Provides various mechanical parameters, process and the equations used for calculation of respective parameters of film.

TABLE- 7

VARIOUS MECHANICAL TESTS USED FOR CHARACTERIZATION OF ORAL THIN FILM

Mechanical test	**Method**	**Equations**
Thickness	Vernier Callipers scale	Calculate the standard deviation by noting the film sample's thickness at five different locations (the centre and four corners).
Tensile Strength	Brookfield texture analyzer was used to determine tensile strength of film. Film sample is fixed between the two clamps and	$TS=\frac{\text{Failure load}}{Strip\ thickness \times Width\ strip} \times 100$

	the force at which film break down is determined.	
Percent Elongation (%E)	Film expands which develop strain.	$\%\ E=\frac{\text{Increase in length of strip}}{\text{Original lenth of strip}}\times 100$
Film folding endurance	One sample film is folded repeatedly at the same location on the film until it breaks in order to test the film's ability to collapse.	The folding endurance value is determined by how many times the film has been folded.
Young's modulus	The stiffness of a film is assessed using Young's modulus, which displays the ratio of applied stress to strain in elastic deformation.	$YM=\frac{Stress}{Strain}$
Tear resistance	The initial force necessary to overcome the resistance of the film. At the point of tearing, the maximum force is determined.	It's written as Newton.

5. Stability of oral dispersible film

The stability studies of thin films depend upon water content in film, and the presence of a large amount of water formed makes it more sticky and causes the presence of microorganisms **[119].** On the other hand, a low amount of water reduces the plasticizing effect in film, and crystallization of film affects its biopharmaceutical properties. As a result, the drug in the oral thin film should remain in the amorphous state **[120, 121]**. Stability tests on oral thin films were carried out in accordance with ICH recommendations. Q1AR2 is used for stability studies of new therapeutic ingredients, while A1C is used for 'stability studies of new drug dosage forms' **[122,123]**. Madihamushtaque and a colleague performed accelerated stability studies on oral fast-dissolving thin film of escitalopram. The films were folded using aluminum foil and butter paper and then put in a six-month stability chamber. According to ICH recommendations Q1AR2 (ICH, 2003), samples were taken at 0, 1, 3, and 6 months to evaluate quality features **[59]**. Due to some issues in the stability of oral thin film, it must be packed carefully to prevent moisture or heat degradation.

5.1. Packaging

From the previous research studies, it was reported that oral thin films are sensitive to heat, light, and moisture content. They need the special packaging that protects the film from all these aspects and is also useful for maintaining the film's mechanical qualities. From an industrial standpoint, there are two types of packaging: one is primary, and the other one is secondary. Primary packaging is the one that actually holds the oral thin film, like a peel pouch sachet. These are also called first-level packs. The secondary packaging is called second-level packaging, which holds the primary packaging like, folding cartons **[124]**.A number of elements must be taken into account throughout the film packaging process, including barcode labeling, the content of usage instructions, and child-resistant closing. The most often utilized packing material is aluminum pouches. But these days, alternative materials, like blister cards, plastic pouches, foils, and papers, are also used to package films **[6]**. APR-Rapid Labtec's card is a patented packaging innovation that is primarily made for Rapid films. The Rapid card has three films on each side, is the size of a credit card, and allows you to pack each dose separately **[43]**. **Figure 7** illustrates various types of packaging of oral thin film. Prajapati et al. reported pullulan-based zolmitriptan films that were tightly packed into aluminum sachets **[125]**. Similar to this, Dixit and Puthli created several different types of packaging systems, including dispensers with the ability to dispense multiple units and multi-unit blisters **[44]**.

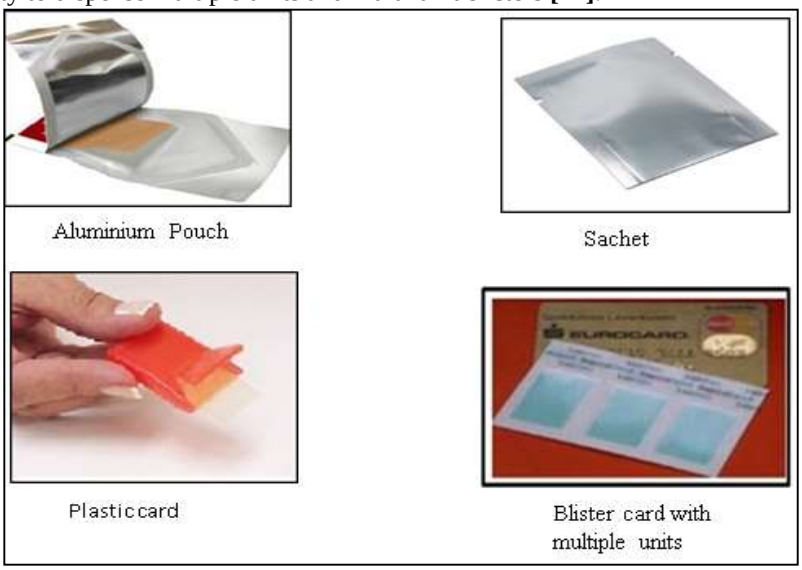

Fig.7. Various types of packaging of oral thin film

6 Patent and clinical trial

The vast majority of the literature review is based on patents for various oral thin films from a variety of patenting bodies around the world, including the World Intellectual Property Organization, The European Patent Office, and the Indian Patent Office. The United States Patent and Trademark Office granted the most patents for medications like sildenafil citrate, acetaminophen, buprenorphine, dextromethorphan, and naloxone (USPTO) **[126].** A patent on oral thin film was recently filed by an Indian company such as Monosol Rx, Warner Lambert, and LTS Lohmann, and other Indian pharmaceutical businesses such as MonoSol Rx, and Warner Lambert have also filed patents on oral thin film in the Indian Patent Office (IPO). Section 505(b) refers to the oral thin film as a "new dosage form." **[127]**. As a result, we concentrated on spotlighting the key Indian manufacturers who are working in this area and have been given patents on oral thin films, as well as worldwide patents (under the PCT) **[128]**. Table 8 lists the title/abstract, patent number, and findings.

TABLE- 8
PATENT ON ORAL THIN FILM

Patent no	Title	Abstract	Ref
US20250090475A1	Drug-loaded amino acid-based poly(ester urea) films for controlled local release of non-opioid analgesic compounds	This invention offers a drug-loaded poly (ester urea) film based on amino acids for regulated local delivery of non-opioid analgesic compounds, as well as various manufacturing and application processes.	129
US2020146997A1	Films and drug delivery systems made there from	The invention provides details of an oral thin film exhibiting uniform heterogeneity that is not self-aggregating.	130
US10918602B2	Compositions and methods for preparing polymeric films loaded with uniformly distributed drug particles	By utilizing greater surface-modified micronized drug and film-forming precursors, enhanced/efficient drying techniques, and increased content uniformity of active pharmaceutical agents, the present disclosure provides improved systems for fabricating film-based pharmaceutical products.	131
US11464736B2	Thermally gelling drug formulations	The currently disclosed orodispersible films are produced by a solvent casting process, in which a mixture of a thermoresponsive polymer is cast at a temperature to produce a stable gel, which is then evaporated to produce a thin film.	132
US11207805	Process for manufacturing a resulting pharmaceutical film	The film products and methods used to prepare them that show non-self-aggregating uniform heterogeneity are the subject of the invention. The films are created via a regulated drying process or another method that preserves the necessary uniformity of the film, and they dissolve in water.	133
US2019380973A1	Uniform films for rapid-dissolve dosage forms incorporating taste-masking compositions	The current invention is directed to thin delivery systems films that disintegrate quickly for oral administration of active ingredients. The active ingredients are offered as taste-masked or coated particles with regulated releases that are evenly dispersed throughout the film structure.	134
US11021437B2	Pharmaceutical formulation for sublingual or buccal delivery of epinephrine or a prodrug thereof	In one embodiment of the invention, a quickly dissolving film serves as the delivery vehicle for a pharmacological composition for the treatment of anaphylaxis.	135
US2022296567	Oral dissolvable film that includes plant extract	The thin film disclosed in this invention has the ability to accelerate the beginning of action, reduce dosage, and improve the active ingredient's effectiveness and safety profile.	136
US2022346436	Orally dissolving films	The present invention is an edible film-based oral product. A binder with a minimum weight percentage of 30%, a plasticizer with a minimum	137

		weight percentage of 5%, and an active ingredient can all be found in an edible film that is orally soluble.	
US2022409584	Stable tryptamine oral films	The creation of oral film dosage forms containing tryptamines, and ideally psilocybin, is the focus of this disclosure, which relates to oral film dosage formulations and procedures.	138
WO2022011246	Method and system for manufacturing oral soluble films, compositions of oral soluble films, oral soluble films made thereby, and methods of use thereof	In this invention, an oral soluble film with at least one active ingredient is described.	139
US2021369602A1	Oral care compositions comprising benzocaine and mucoadhesive thin films formed therefrom	An oral care compound is offered by the current invention. The compositions might be offered in a film-like solid form. One or more film-forming polymers, one or more bioadhesives, one or more plasticizers, benzocaine one or more polymeric solvents, and a hydrophilic solvent can all be included in the compositions.	140
US11173114B1	Method and system for manufacturing oral soluble films and orally soluble films made thereby	This patent describes an oral soluble film with at atleast one active ingredient present in it . Alternately, a multi-layered film has a number of layers, at least one of which is an oral soluble film layer that contains at least one active ingredient.	141
US11524058B2	Oral dissolving films containing microencapsulated vaccines and methods of making same	A film that dissolves in the mouth and is made of bioactive substances that are nano- or microencapsulated is described in the invention. A solution comprising nano- or micro-encapsulated bioactive material, a crosslinking agent, and a photoinitiator may be dispensed into a number of wells in a tray using a 3D printer to create the film. Radiation is used to crosslink the material after it has been administered, creating a film.	142
US2020170994	Sublingual cannabinoid compositions	The current invention offers unique sublingual muco-adhesive cannabis compositions in the form of sublingual tablets or films, demonstrating better bioavailability, stability and decreased side effects such as irritability.	143
US2019350876A1	Oral thin films comprising plant extracts and methods of making and using the same	The current disclosure offers cannabidiol-containing formulations as well as techniques for producing and using them.	144
US11021437B2	Pharmaceutical formulation for sublingual or buccal delivery of epinephrine or a prodrug thereof	The films include epinephrine or a brand-new epinephrine prodrug for effective, quick anaphylactic therapy in a patient. This invention relates to pharmaceutical preparations that are created by altering epinephrine's physicochemical properties to increase its permeability across biological membranes (sublingual and buccal membranes)	145
US2016184439A1	Orally disintegrating film preparation containing donepezil or pharmaceutically acceptable salt thereof, and preparation method therefor	The oral dissolving film formulation for the treatment of dementia is especially mentioned in the present invention, along with a technique for making such a formulation that contains donepezil.	146

US9763879B2	Oral film containing opiate enteric-release beads	The invention describes an oral wafer or edible oral film dosage for opiate medication administration that is controlled release and abuse-resistant that can be used to treat pain and substance misuse. The enteric-release beads are disseminated in a polymer matrix in the controlled-release layer of the drug delivery oral wafer or consumable oral film dose.	147
US11497783B2	Ingestible films having substances from hemp or cannabis	These mucosally soluble films come with a matrix, one or more hemp- or cannabis-derived active agents, and the matrix itself. Additionally, the disclosure describes how to make such a film for use in pharmaceutical and nutraceutical applications.	148
US2019336453A1	Oral dispersible film compositions	It is discussed how to produce pharmaceutical and nutraceutical compositions utilizing twin-screw hot melt extrusion to create oral dispersible films.	149
WO2012097763A2	A carrier for oromucosal, especially sublingual, administration of physiologically active substances	The invention provides a vehicle for oromucosal delivery of physiologically active compounds, particularly sublingual administration.	150
US20250000813A1	Oromucosal nanofiber carriers for therapeutic treatment	The current disclosure relates to oromucosal nanofiber carriers for active agent delivery that are mucoadhesive or contain a mucoadhesive agent, including ingredients for their preparation, preparation techniques, and usage techniques.	151

6

.1 Clinical trials

In addition, as shown in Table 9, a variety of oral thin films have been developed at various stages of clinical testing. Various manufactures, like Pfizer's Upjohn, Cross Research S.A., Indivior Inc., Aquestive Therapeutics, AstraZeneca, and CMG Pharmaceutical Co. Ltd., performed clinical trials on orodispersible films. **[171]**.

TABLE- 9

TRIALS IN CLINIC (ONGOING, COMPLETED, TERMINATED, AND WITHDRAWN).

Condition	**Interventions**	**Research done by**	**Phase**	**Status**
Bioequivalence	Riluzole	ClinicaCross Research SA	I	Active, not recruiting
Healthy	Sildenafil citrate	Pfizer's Upjohn	I	Withdrawn (transferred to Viatris)
Opioid disorders	Buprenorphine and buprenorphine/naloxone	Indivior Inc	II	Completed
Erectile dysfunction	Sildenafil	Laboratories Genèvrier	Not given	Completed
Healthy participants	Ondansetron	Aquestive Therapeutics	I	Completed
Amyotrophic lateral sclerosis	Riluzole	Aquestive Therapeutics	II	Not completed
Schizophrenia	Aripiprazole	CMG Pharmaceutical Co. Ltd	I	Completed
Safety & bioequivalent studies	Anastrozole	AstraZeneca	1	Completed
Amyotrophic lateral sclerosis	Riluzole	Aquestive Therapeutics	II	Terminated (no longer required)
Sialorrhea	Tropicamide			Completed

Future perspective and conclusion

The versatility of the oral dispersible film platform allows for future applications in a variety of areas, including pharmaceuticals, medical, and biopharmaceutical markets. Additionally, there will be a chance to extend the revenue life cycles of existing drugs whose patents are set to expire and will shortly be susceptible to generic competition. Several drawbacks of older conventional drug delivery systems, including poorer bioavailability, discomfort of administration, and patient resistance, have prompted the development of novel polymeric thin films as an innovative drug delivery technique. The majority of today's formulations are quick-dissolvable tablets, although orodispersible films are more appealing because of their ease of administration, mobility, and increased patient compliance. Overall, these formulations are the most promising and forward-thinking dosage form for delivering medicines and nutraceuticals. Oral dispersible film technology is also the most acceptable and accurate type of oral dosing since it bypasses the hepatic system and provides a better therapeutic response. In addition to being used as pharmaceutical films, they can be used as mouthwashes. This one-of-a-kind technology is growing in both the Indian and international markets, with billions of dollars gained from its emergence in the pharmaceutical, food, and confectionary sectors. This technology is an excellent tool for managing a product's whole life cycle. The future of oral dispersible films appears to be very promising as new technologies are quickly introduced.

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