# Oral films- A comprehensive review

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**Abstract**

Recent trends on the oral drug delivery system targeted for faster drug delivery which can help patient to handle the dosage form conveniently and custom-made dose with more patient compliance. This attracts the researchers focus on oral film technology, the popularity of oral film technology is due to ease of administration in pediatric and geriatric patient. It can give quick onset of action, prevent first pass metabolism, improve patient compliance and convenient to handle. Oral film technology also serves as platform to tailored drug delivery based on the patient requirements and meet the unmet needs of the other delivery system. This review tours the introduction to oral films and its different terminology used in current trends, anatomy of the mucosa and drug delivery system through oral mucosa, Components used in the formulation and its uses, different manufacturing techniques used for manufacturing of oral films, Innovative technologies available in the market for oral film making, Quality evaluation techniques, glance on clinical trials and regulatory pathways, Oral films available in the markets and its comprehensive lists. Oral film technology is the emerging technology which regulatory acceptance demonstrates the scopes of new product developments in pipeline. Global growth of the oral film markets shows steady opportunity for the researchers to explore the technology.

**Keywords:** oral films, mucosa, buccal, transdermal

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## 1. Introductions to oral films

Administration of most drugs to local and systemic circulation using various routes includes Enteral and Parenteral routes, the route of administration by enteral or oral is most viable and popular. which was the traditional and conventionally used for longer time[1]. Oral route has the advantages that can accommodate a versatile range of drugs with good patient compliance[2]. Approximately 80 - 90% of the Active pharmaceutical ingredients are being orally administered, this route was considering popular due to lot of factors such as ease to administrate, Cost effective and highly patient compliance and safety. Oral drug delivery includes various dosage forms such as Solids (tablets, capsules, etc), liquid (syrups, suspension, etc)[3]. Recent trends and development focused on fast dissolving drug delivery of oral solid dosage forms were the Oral dispersible tablets, mouth dissolving tablets and Oral dissolving films. Oral films were remarkable innovation for fast drug delivery system, which can be carry and swallow easily. Major drug regulatory agencies refers oral film as"A thin film that readily dissolves in the oral cavity is commonly referred as orodispersible film" by the European medicine agency or "Simple soluble film" by USFDA[4]. The schematic diagram of the Oral film and their function area of the action are capturedin figure **1**.

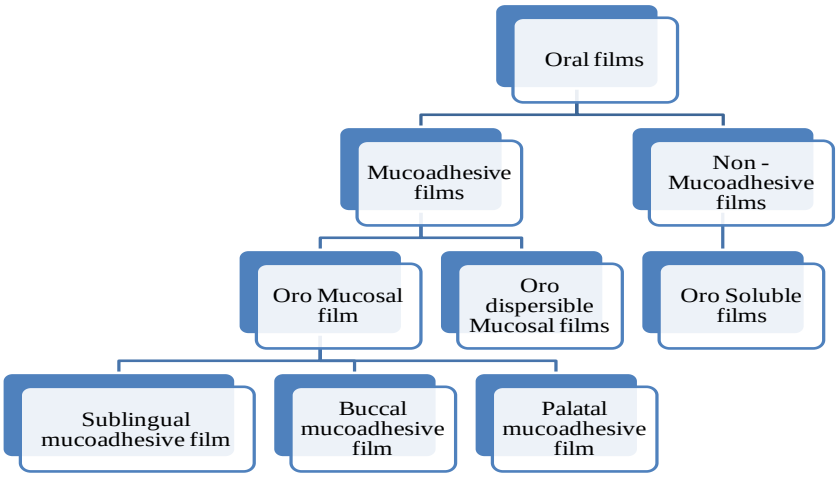


***Figure 1: Schematic representation of the oral film and their types.***

a. Different type of buccal films and terminology in current trends[5,6]

Different terminologies were used for oral films with their advantages and physical nature of films. The following are the various names found in literatures for oral films as Oral thin film, fast dissolving film, oral strips, Oral disintegration film, mucosal adhesive film, buccal film, thin film, wafer, Trans mucosal film, or dispersible film, buccal soluble film, and soluble film.[7]

b. Advantages:

i. Pharmaceutical companies have created a variety of dosage forms for intraoral delivery, including lozenges, chewing gum, sprays, buccal solutions and gels, and oral films (OF).

ii. Easy of administration without water
iii. Risk of choking can be avoid in the use of elders and younger patient
iv. Convenient to handle the dosage form
v. Taste masking can be done for bitter drug products.
vi. It is applicable to both local and systemic pharmacological effects.
vii. You can get a quick start to action.
viii. It improves patient compliance
ix. One can prevent first pass metabolism.
x. Clinical complexity can be avoided. [8,9]

c. Disadvantages
i. Drugs with buccal instability and buccal instability cannot be formulated in oral film
ii. High dose drugs cannot be incorporated in the oral films
iii. Stability of the oral films are considerably low compared to conventional solid dosage form
iv. Specialized equipments and sophisticated system required for manufacturing and analysis.
v. Uniformity of the dosage form might be critical in the dosage form.
vi. Expensive packaging systems are required.[10,11]

**2. Formulation components**

a. Active Pharmaceutical ingredients

Oral film technology can accommodate variety of active pharmaceutical ingredients in the platform to deliver the drug to local and systemic circulation. Oral film delivers both the water-soluble drug in solution form and water insoluble drugs in dispersed form. Wide ranges of therapeutic category drugs like antihistamines, anticonvulsant, antidiabetic, anti-arrhythmic, antifungal, antibacterial, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, and multivitamin can formulate in oral film. [12, 13]

Ideal properties of drugs which can be used for oral film

- Low dose drug is likely to incorporate in the ODF.
- High lipophilic drugs log P >2 can be formulated in the ODF
- Soluble drugs can be easily manufactured in the ODF.
- Drugs which are unionized at mucosal pH can be formulated as ODF.
- Small molecules drugs less than 800Da can be incorporated in ODF.
- Drugs which have palatable organoleptic characters and non irritant can easily design into oral film.
- Drugs which withstand high temperature can design into oral film by hot melt extrusion technology. [14]

b. Hydrophilic polymers

A wide range of polymers can be used for the manufacturing of the oral film; the polymers act as the backbone and platform for the delivery system carry the drug and other components into the delivery site. The ideal characteristic of the polymers to select for the oral film is one of the most critical factors. The polymer must be

- Nonirritant and Non toxic
- Palatable in taste
- Must hydrate on release the drug on the application site
- Compatible with the oral mucosa
- Should have adequate tensile strength and stability over the shelf life.
- Polymer must be easily available and inexpensive.
- Fast dissolving film must disintegrate or dissolve quickly to give pharmacological action.

In general, polymers were divided into three categories: natural, semi-artificial, and synthetic polymers.

Natural polymersare obtained fromnatural source like pullulan, gelatin, modified starches, chitosan, Loctus bean gum, xanthan gum and guar gum etc.

Semi synthetic polymersare cellulose derived polymers like Hypromellose and hydroxypropyl cellulose, sodium alginates and POE etc. [15]

**c. Plasticizers**

Plasticizer is important component These aids in enhancing the strips' suppleness and lowering their brittleness. It increases the strips' tensile strength, elongation, and stretching propensities. It also improves their mechanical strength. By lowering the polymers' glass transition temperature and enhancing their melting characteristics, plasticizers raise the quality of the strip. Generally plasticizers used from ranges of 0- 20% of the dry weight of the polymers in the formulation depends upon the requirements. [16,17]

**d. Absorption / Permeability enhancers[18]**

Permeability enhancers are the substances which improve the permeation of the drugs through the epithelia cell into the systemic circulation. Drugs are absorbed more easily across the buccal mucosa when permeability enhancers are utilised, which increases the bioavailability of the medicine that has been delivered.

**e. Flavors**

Flavors are the components which improve the smell and taste of the dosage form. As oral strips were intended to administer to oral cavity, palatability of the dosage for is more important criteria for patient acceptability. Generally favors are natural, semi synthetic and synthetic compound. The type of medicine will also influence the flavour choice.Fruit flavor like orange, lemon, apple, pineapple, peach and berry flavors are generally selected for kid products and refreshment flavor like mint, clove, cinnamon,

mint, coffee, tea, cola and vanillin etc were selected for adult's products. Cooling flavor is used to have cooling sensation for mouth. They work by producing their own tastes and odours and acting as anaesthetics on taste-related sensory receptors.

**f. Sweeteners**

To hide the bitter flavour of the formulation and increase consumer acceptance of the drug product, sweeteners are employed. Generally sweet taste is important in the pediatric drug product. In the oral films, sweeteners are employed both naturally and artificially. The formulation includes natural sweeteners such fructose, glucose, mannose, galactose, ribose dextrose, and maltose. Artificial sweeteners such as aspartame, acesulfame potassium, saccharin sodium, sucralose and neotame were also used in the formulation.

**g. Saliva simulating agents or buffers**

Salivating agent are the compound which increase the rate of salivation production and improve the formulation disintegration and drug solubility. Acids like citric acid, ascorbic acid, lactic acid, maleic acid, tartaric acid, etc. are typically utilised as saliva-simulating agents.

**h. Coloring agents**

Coloring agents were used to make the oral film palatable for patients. It includes Natural coloring agents like anthocyanin, caramel, carotenoid, chlorophyll and curcuminoid etc. Synthetic colorants are both organic and inorganic colorants. These colorants were used in very low concentration to the oral film.[19]

## 3. Manufacturing techniques

Conventional method of manufacturing of the oral films by two methods: 1. Casting method and extrusion method. From the fundamental casting technique, hybrid casting is next, followed by semisolid solvent casting. Similar to extrusion, solid dispersion is a subset of hot melt extrusion. [20] A schematic representation of the conventional method of manufacturing of the oral film is presented in below.

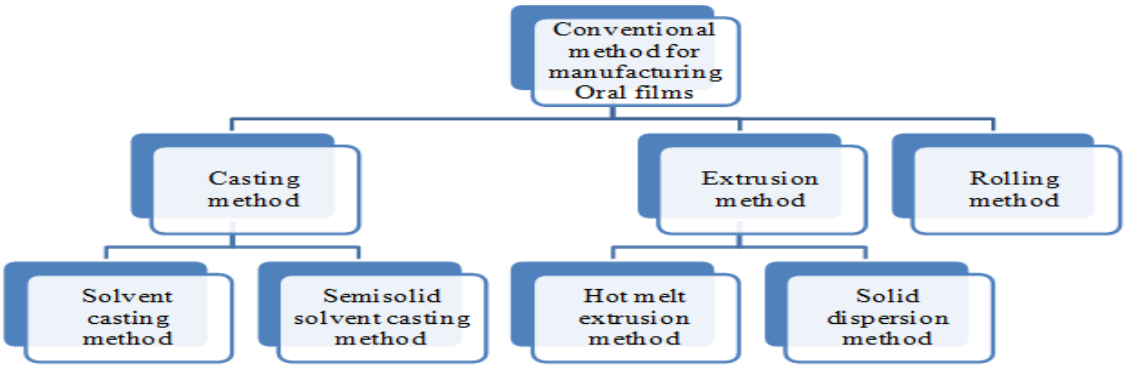


***Figure 2: Schematic representation of Manufacturing techniques.***

**a. Solvent casting technique**

One of the most often employed conventional procedures for the preparation of the ODF is the solvent-casting method. The API and other components are solubilized in the appropriate solvents while being stirred to create a clear viscous solution in this process. Make sure the soluble compound is soluble and the insoluble compound is evenly dispersed to create homogeneity in the contents. Vacuum used to remove the entrapped air and de-aeration is important to maintain the uniform film thickness and film properties. The created mixture is cast into a film, allowed to dry, and then cut into the required size pieces. The solvent selection is crucial steps in the solvent casting techniques, this also depend upon the physical and chemical properties of the selected API. These characteristics include the API's compatibility with other film-forming excipients, its compatibility with solvents, the API's polymorphic nature, and its sensitivity to temperature. To control the impact of moisture, additional precautions must be taken during ODF manufacturing and packing. The solvent-casting method of producing ODF is shown schematically in Figure. The presence of moisture considerably affects the film's mechanical characteristics and stability. Temperature is another aspect that needs to be strictly controlled. The solution's viscosity and the API's temperature sensitivity must be maintained under controlled temperature conditions. Pouring the solution over an inert foundation requires a certain kind of equipment, such as rollers. The needed film thickness is determined by the distance between the roller and the substrate. The solvent is removed from the film during the final process of drying it, and the semi-solid casting technique aids in producing the finished item. Typically, an inert basis for film casting is made of glass, plastic, or Teflon plates. Several issues might arise when manufacturing technology is scaled up from the laboratory to the production level. The casting of the film, achieving a uniform film thickness, and adequate sample drying are a few examples of these issues. In the final stage of drying, the appropriate dryer type must be chosen. Following the drying of the films, cutting, stripping, and packaging are completed. Films of the appropriate size and shape can be cut. The most frequent film sizes are 3 x 2 cm2 and 2 x 2 cm2. The container for packing that is chosen is a crucial parameter for the ODF. The packaging should have enough mechanical strength to shield the film from outside elements like temperature and humidity as well as during delivery. Single-unit containers and multiple-unit dispensers can be chosen based on the properties of the packaged films are inspected before being packed into a secondary packaging container. [23,24]

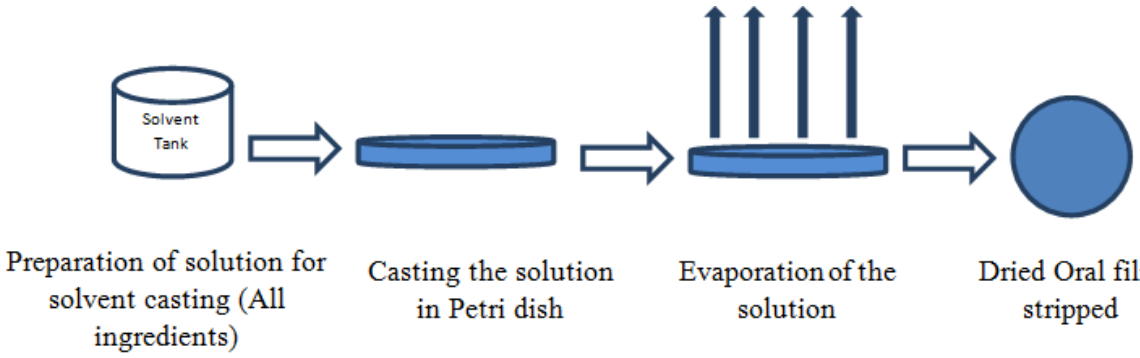


***Figure:3*** *schematic process of the ODF manufacture using the simple solvent-casting method.*

**Advantages**

Solvent-casting is the best method for producing films incorporating heat-sensitive APIs because it requires lower solvent removal temperatures than a hot-melt extrusion process.

Better thickness homogeneity and bitter clarity than extrusion,

Film has a fine gloss, is free of flaws like lines, is more flexible, and has greater physical qualities.


Process flow chart for Solvent casting method.

**b. Hot melt extrusion**

Granules, sustained-release pills, and transdermal and transmucosal drug delivery systems are frequently made with HME. The HME process recently has acquired appeal in the pharmaceutical business. Formulators can extrude mixtures of pharmaceuticals, polymers, and plasticizers into different final forms to produce desired drug-release patterns using knowledge from the plastics industry. By using this method of processing films, a polymer is shaped into a film using the heating process as opposed to the conventional solvent-casting method.

The API and other excipients are combined in a dry condition for the HME process before heating is initiated and the molten mass is extruded from the hot-melt extruder. The total removal of the solvent is a benefit of this method. The films are cut to the required size after being given time to cool. The technique is suitable for thermostable pharmaceuticals due to the high temperature employed in it.[25] This procedure prohibits the use of medications that are temperature sensitive.

HME has the following benefits for film formation:

- No need for solvent or water
- Fewer processing steps good dispersion mechanism for poorly soluble drugs
- More uniform dispersion of the fine particles due to intense mixing and agitation
- Less energy compared to high-shear methods

- Minimal product waste Scalability
- Good control of operating parameters
- Processes of preparation of oral film by Hot melt extrusion

**c. Solid dispersion extrusion**

When one or more APIs are dispersed using techniques like HME in the presence of amorphous hydrophilic polymers in a solid state in an inert carrier, this is referred to as solid dispersion. Immiscible components are extruded with the medication in this process, and solid dispersions are subsequently made. Finally, using dies, the solid dispersions are formed into films.

Using techniques like HME, one or more APIs are dispersed in a solid state in the presence of amorphous hydrophilic polymers. This process is referred to as solid dispersion. Immiscible components are extruded with the medicine in solid-dispersion extrusion, creating solid dispersions. By using dies, the solid dispersions are formed into films. In a suitable liquid solvent, the medication is dissolved. Without removing the liquid solvent, this solution is added to the melt of polyols, such as polyethylene glycol, produced below 70 °C. The chosen solvent or medication in solution might not melt with the polyethylene glycol. The liquid solvent utilised may have an impact on the drug's polymorphic form that precipitated in the solid dispersion.

**a) Rolling method**

The rolling method involves rolling a drug-containing solution or suspension on a carrier. Water and an alcohol-water mixture make up the majority of the solvent. The film is cut into the desired shapes and sizes after it has dried on the rollers. In the rolling method, a solution or suspension containing the drug is rolled on a carrier. The solvent is mainly water and a mixture of water and alcohol. Thefilm is dried on the rollers and cut into desired size and shapes. Making the film involves making a premix, adding the API, and then forming the film. The master-batch feed tank is filled with the premix, also known as the master batch, which contains the film-forming polymer, polar solvent, and additional excipients besides the API. Through a metering pump and control valve, a predetermined amount of the master batch is regulated and delivered to the mixers. Through an aperture, the needed quantity of the medicine is added to the preferred mixer. The API and master batch are blended to create a homogenous matrix, which is then fed to the pan using metering pumps. A metering roller is used to manage the film's thickness. Finally, the film is created on the substrate and removed using the support roller. The wet film is dried using controlled bottom drying, preferably in the absence of external air currents or heat on the surface of the film.


**a) Spray technique**

Spray technique involves spraying the slurry or solution into a definite concentration in a designed place and followed by drying of the solvent from the solution to form a film.[25]


**3D printing techniques**

By overcoming the drawbacks of existing FDF manufacturing techniques, three-dimensional (3D) printing may become a viable option for the development and manufacture of desired FDFs. 3D printing has been used in the development of complex oral dosage forms and at commercial scale to produce Spritam® fast dissolving tablets. In particular, the hot-melt extrusion process is more similar to fused-deposition modelling (3D printing). To create several oral medicine administration methods, FDM 3D was used.

Filaments are used by traditional FDM 3D printers to create the desired objects. The filament in this apparatus travels through a thin tubing system and a 3D printerhead's moving pulleys and gears. The filament is heated and extruded through a nozzle with a small diameter in this instance (typically 0.4 mm). FDM 3D printers can create items with repeatable dimensions, especially when uniform-diameter filaments are utilised (low diametertolerance). If the filament diameter is inconsistent (either too wide or too thin), the extruder will either not operate properly or the printed product will have uneven dimensions and weight.

Consequently, FDM 3D may enable the production of FDFs with repeatable dimensions and physicochemical characteristics. Additionally, FDM 3D offers the chance to laminate more than one layer into a film. [26]

## 4. Innovative technologies on Oral Films:

Generally majority of the top companies likely to develop their own new innovative technology platform to produce the oral film. The choice of technology must consider the wide range of medication candidates and is likely to change depending on the physiochemical makeup of the active ingredient and the desired characteristics of the finished dosage form. Oral film

technologies help the companies to improve the existing drug formulation into new dosage form which helps the product life cycle management. [27]

The following are the innovative technology platform use for manufacturing of the oral films.

**1. Pharmfilm:**

Pharmfilm is a Monosol-protected medication delivery system. One of the first businesses in the oral film sector was Monosol. With a loading capacity of up to 80 mg, it offers a more reliable and steady dosage than other traditional dosage forms. According to Monosol, the rapid soluble drug delivery system and buccal medication delivery may both utilise this technology platform. As a quick drug administration system, Zulpenz (ondansetron hydrochloride) oral film had been successfully integrated with the Pharmafilm technology. Suboxone sublingual film was created by Pharm film Technology as a delayed sublingual release drug delivery device Sympazam (Clobazam) oral film 5, 10, and 20 mg is a benzodiazepine recommended for adjunctive treatment of seizures related to Lennox-Gastaut Syndrome (LGS) in individuals 2 years of age and older. A provisional US patent application for "Nanoparticle Film Delivery Systems" has been filed by MonoSol Rx, the industry leader in developing and manufacturing pharmaceutical films based on its proprietary PharmFilm® drug delivery technology, and Midatech Group Ltd., a global leader in the design, development, synthesis, and manufacture of nanomedicines. The therapeutic applications of proteins and peptides based on nanoparticles that are given in pharmaceutical films are the focus of the applications filed with the United States Patent and Trademark Office (USPTO). A soluble film formulation of the benzodiazepine diazepam called LIBERVANTTM, a product line of Aquestive Therapeutics, is administered buccally, or inside of the cheek. It is intended for the rapid treatment of acute, uncontrolled seizures in selected, refractory patients with epilepsy who are on stable regimens of AEDs and who need intermittent use of diazepam to control episodes of increased seizure activity. The LIBERVANTTM was accepted by the FDA as a New Drug Application (NDA) and is currently undergoing required review. Phase I and preclinical/proof of Concept stages, respectively, are reached by AQST-108 and AQST-305. [28,29]

**2. Rapidfilm®**

Another unique technology created by Labtec GmBH is Rapidfilm®. Orodispersible film (Ph.Eur., EMA), also known as Rapidfilm®, and soluble film (FDA): Oral film, thin strip, flash-release wafer, quickly dissolving film, quickly dissolving oral thin film, and oral film The ideal formulation for treating patients who are old or children is Rapidfilm® Technology. Rapidfilm® is a water-soluble, fast-dissolving thin film that is non-mucoadhesive and comes in single- and multilayer drug design systems. The first oral Rx film to receive approval worldwide was the ondansetron Rapidfilm®.[30] According to US Patent US8580830B2, ondansetron or a pharmaceutically acceptable salt of it, along with a hydrophilic binder and

water-soluble diluents, can be used to create an orally disintegrating film that is non-mucoadhesive and capable of dissolving upon contact with saliva in the buccal cavity within about sixty seconds. [31] Zolmitriptan Oral Dispersible Film has been submitted for approval in Europe by APR Applied Pharma Research and Labtec GmbH. (ODF). A key chemical in this therapy is donepezil, which has been authorised by the U.S. Food and Drug Administration (FDA) and the majority of European nations for the symptomatic treatment of Alzheimer's disease. [32]

3.**Smart Film®**

The Smart Film® technology, created by Seoul Pharma, is an oral film with a high loading dose capacity of over 140 mg that can include both hydrophilic and hydrophobic pharmaceuticals. It also has a unique taste-masking technology and an environmentally friendly manufacturing process (Water based solution). In 2012, this South Korean pharmaceutical company introduced Vultis®, a 140.45mg film version of sildenafil citrate, to the Korean market. The magnesium oxide and sodium hydroxide used in the Sildenafil SmartFilm® technology's fast-dissolving film composition hide the drug's unpleasant taste. [33,34] Tadalafil 5, 10, and 20 mg oral film for erectile dysfunction called Vulteum ODF was introduced in 2014. Donepezil Hcl 5 and 10 mg Alzheimer's disease medication Artpezil ODF was introduced in 2016. Aripiprazole, Solifenacinsuccinate, SPO-1405, SPO-1705, SPO-1706, and SPO-1801 are among the products in the R&D pipeline. [35]

**4.VersaFilm™**

Intel Genx Technologies Corp. created and trade marked the Versa FilmTM technology.

VersaFilmTM is presently employed as the system of choice for indications needing an immediate commencement of action. It was originally created as an edible film for the instant delivery of savoury flavours to food substrates. According to the business, VersaFilmTM can be sublingual and its disintegration duration can range from 30 seconds to 10 minutes, depending on the application. About 40mg is the maximum medication load stated. [36,37] Several pharmacological compounds are being considered for or integrated into the VersafilmTM technology, per the IntelGenx pipeline. However, just one, the Rizatriptan VersaFilmTM, an oral fast release film for migraines created in collaboration with Red Hill Biopharma Ltd., has recently gotten a thorough response letter from the FDA. Other medicines in development include Buprenorphine/Naloxone, Cannabinoids, Psilocybin, Montelukast, Loxapine, which was granted a Canadian patent, and Psilocybin. [38]

**5. Bio-FX® Fast-Onset Oral-Cavity ODF**

The Bio-FX® Fast-Onset Oral-Cavity ODF from NAL Pharmaceuticals Ltd. is another technology platform. It is an oral film that has been designed using the Bio-FX® absorption enhancer system, which promotes the absorption of pharmacological substances through the oral mucosa with the goal of enhancing oral bioavailability of pharmaceuticals by preventing first-pass metabolism and gastrointestinal degradation. To enhance taste and tongue feel, this

technology also includes a specially built taste-masking mechanism. The following ODFs are in development: NAL1606 Rizatriptan ODF for Migraine, NAL2762 Nicotine ODF for Smoking Cessation, NAL8233 Tadalafil ODF, NAL8238 Sildenafil ODF for Erectile Dysfunction, NAL6013 Levocetirizine ODF, and NAL6336 Montelukast ODF for Respiratory Allergy. [39]

**6. Quicksol®**

The oral film platform from SK Chemicals known as Quick Sol® technology can accept a wide range of medicinal ingredients. According to the company's pipeline, various drug substances were loaded, but only two are already on the market, Montfree (Montelukast)ODF and Mvix-S (Mirodenafil) ODF. Mvix-S is a 50 mg oral film that is thin, light, and portable that was introduced in January 2012 and has a 16.7% higher mirodenafil absorption rate than the Mvix tablet. In addition, Mvix-S sold over 1 billion units 15 days after its release. [40]

**7. Xgel**

The intellectual property of Meldex International is based on the Xgel™ film technology, which is utilized in all of its film systems, including Soluleaves™, Foam burst TM, and Wafertab™. The Soluleaves ™ platform can be tailored to release a pharmacological ingredient quickly or to attach to the oral mucosa over time. The Foam burst ™ is a variation on the prior technique in which an inert gas was included during the film's production, creating a honeycomb structure that regulates the pharmacological substance's pace of breakdown and creates a novel mouth feel. The Wafer tab ™ platform, on the other hand, is made from a placebo Xgel ™ film, to which the medicinal material is put later to avoid exposure to excess heat and moisture. The creation of multilayer films and the production of unstable medications are both made possible by this technology. Nicotine Soluleaves™, which Meldex was developing in 2007, have not undergone any current developments. This oral film is based on cellulose derivatives, per the patent information.

**8. Thinsol™**

Additionally, BioEnvelop (or Paladin Labs) has its own patented technology, the ThinsolTM, an oralfilm based on carboxymethylcellulose that has been digested by enzymes. This platform is a quick-dispersing film (dissolves in five to thirty seconds), allowing a drug loading of up to 60% and including pharmaceuticals that are sensitive to heat because it may be dried at moderate temperatures. Two supplements—vitamin B12 and melatonin—are produced and packaged by ODF Nutra as oral strips by Jamieson Laboratories. ODF Nutra is in possession of numerous marketing licences. The company introduced its own line of natural health products, including the Nutra-Strip and Octane Boost energising strips, which come in six flavours.

**9. Meltfilm or Schmelzfilmen**

Olanzapine, sildenafil, donepezil, and risperidone are the four currently marketed medications under the brand name "Schmelzfilmen," which was created by Hexal. The four formulations have slightly different compositions, but overall, they are all cellulose-based films. According to

the commercially available Olanzapine oral film, ethyl cellulose serves as the primary film-forming polymer and is plasticized using dibutyl sebacate. However, the proportions mentioned in the patent claims seem to suggest that HPMC can also be utilised as a film-forming polymer[41]

**10. Eluting Bandage Platform**

The Eluting Bandage Platform, an original and patented oral film platform, is owned by Pharmedica. This is a platform with a variety of characteristics that can be employed as a single layer or several layers, with quick disintegration or gradual disintegration, and for combination or protective treatment. The Eluting Bandage Platform is a versatile and multifunctional tool that may be used for a wide range of items, from prescription medications to fresh breathers. For the prospective treatment of diabetes, Pharmedica was creating oral insulin formulations, with a launch date for 2013 expected. There isn't any other information available, but the company's website lists insulin and cannabis as prospective products for the Eluting Bandage platform.

**11. Orally and Adhesive Disintegrating Films**

The Japanese business KyuKyu Pharmaceuticals Co. LTD also has its own oral film platform technology. KyuKyu has two distinct technologies, the "Orally

The "Adhesive and Disintegrating Film," which dissolves in 10 to 30 sec

Disintegrating Film" is a substance that sticks to the oral mucosa and varies in disintegration time ranging from 30 minutes to 8 hours (KyuKyu Pharmaceuticals Co.). Several oral dispersible films from KyuKyu's extensive pipeline are available on the market, primarily in Asia. Amlodipine oral disintegrating film 2.5 and 5 mg, Donepezil hydrochloride oral films 3, 5, and 10, Loratedine oral films 10, Olopatadine oral films 2.5 and 5, Voglibose oral films 0.2 and 0.3 mg, and Zolpiderm oral films 10 mg are among the oral films that are offered by the company "Rapidly Soluble Film Preparation" Patent US-6906043-B2 The disclosed product is a fast soluble film preparation with high elution rate that primarily consists of a medication, an edible polymer, and a saccharide. "Preparation for film containing medicine with a bad taste" A film preparation according to US20120328675A1 includes coating layers without terpene generated on either side of a layer containing a medication that has an unpleasant taste and a terpene. [42]

**12. Soluleaves$^{TM}$**

The Bio Progress company has developed a unique technology called SoluleavesTM. The active chemicals and tastes in soluleaves are intended to be released immediately upon contact with saliva. Films are therefore ideal for distributing a wide range of goods that need to be released quickly in the mouth. The purpose of SoluleavesTM films is to cling to the mucosal membrane and release the active components gradually over a 15-minute period. This can be utilized for flavour release items like vitamins, candy, and mouth freshener. [43,44]

## 13. Quality Evaluation Techniques

a. Organoleptic characters

Organoleptic evaluation is one of the important evaluations which evaluate the patient acceptability of the oral film. Organoleptic evaluation includes color uniformity, flavor, sweetness and oral disintegration etc It has also been reported on experiments employing electronic tongue measurements to differentiate between the various sweetness levels in taste-masking formulations. [45,46]

**b. Mechanical characters**

**Thickness**

At various well-placed strategic points, a micrometre screwgauge can be used to measure the thickness of a strip. It is crucial to confirm the uniformity of the film's thickness because it has a direct impact on the accuracy of the dose in the strip.

**Dryness test/tack tests:**

It has been determined that there are roughly eight phases in the drying process for films: set-to-touch, dust-free, tack-free (surface dry), dry-to-touch, dry-hard, dry-through (dry to handle), dry-to-recoat, and dry print free. Although the majority of the experiments can be elaborately modified to evaluate pharmaceutical OS, these tests are generally utilised for paint films. The specifics of how these factors were evaluated can be found elsewhere and are outside the purview of this review. Tack describes how firmly a strip sticks to a piece of material (like as paper) after being rubbed on it. For this investigation, there are also instruments available. [47]

**Tensile strength:**

The highest stress that may be applied to a strip specimen before it breaks is its tensile strength. It is computed by dividing the applied load at rupture by the strip's cross-sectional area. Using Eq.(1),one can determine the tensile strength:

$$Tensile\ strength = \frac{Load\ at\ corresponding\ strain}{Cross\ section\ area\ of\ film}$$

**Percent elongation**

A strip sample experiences strain when stress is applied, which causes it to stretch. Strain is essentially the strip's deformation divided by the sample's initial dimension. In general, strip elongation rises as plasticizer content does. Good flexibility and material extensibility are indicated by a high stretch. elongation percentage determined by formulae

$$\%\ Elongation = \frac{Increase\ the\ length\ of\ film\ X\ 100}{Initial\ length\ of\ the\ film}$$

**Tear resistance**

Plastic film or sheeting's tear resistance is a complex function of its ultimate rupture resistance. In essence, an extremely low loading rate of 51 mm (2 in.)/min is used, and it is intended to quantify the force needed to start tearing. The rip resistance value in Newton's units is the highest stress or force—typically obtained near the beginning of tearing—necessary torn the item (or pounds-force).

**Young modulus:**

The elastic modulus, often known as Young's modulus, is a measure of strip stiffness. In the zone of elastic deformation, it is expressed as the following ratio of applied stress to strain:

Hard and brittle strips exhibit a high Young's modulus and tensile strength with little elongation..Young modulus is calculated by formulae

$$Young\ modulus = \frac{Slope}{Strip\ thicknessXCross\ head\ speed} X100$$

**folding tenacity**

Repeated folding of the strip at the same location until the strip breaks is used to measure folding endurance. The folding endurance value is calculated as the number of folds the film can endure without breaking.

**Disintegration test:**

Fast dissolving oral strips are subject to the same disintegration time constraint of 30 seconds or less for orally disintegrating tablets as indicated in CDER advice. Oral rapid dissolving films and strips don't have any official guidelines, although this can be used as a qualitative guideline for quality control tests or during the development stage. For this study, pharmacopoeial disintegrating test equipment may be used. Strips often disintegrate within 5 to 30 seconds.

**c. Chemical characters**

**Dissolution:**

The dissolution method is an important component of the drug product's quality, particularly in terms of the apparatus and media choices. Despite the Pharmacopeia's straightforward orientation, it's crucial to keep in mind that this assay should be representative and a method for forecasting in vivo behaviour.

Regarding the apparatus and settings of the dissolution method, the bulk of the mentioned procedures fall short of accurately simulating physiological conditions.

Orodispersible dosage forms, such as orodispersible tablets, or transdermal dosage forms, which frequently use attachments to lock the dosageform in the bottom of the vessel, would generally be the two assumptions on which the equipment would be chosen. More people utilise the paddle equipment (USP type II) than the basket apparatus (USP type I). However, several studies have advised the use of modified apparatus due to the shortcomings of both

approaches. Most of the alterations involved reducing the volume of the dissolution media (typically involving vessel type modifications), changing the stirring accessories, and changing the type of dissolution medium, such as simulated artificial saliva.

Another strategy is to use a paddle over disc device (USP type V). A gastric pH dissolving media and this dissolution equipment were both utilised in the development of Zuplenz®. Since the primary goal of this fast-dissolving film is to quickly dissolve in the mouth so that it can be easily ingested with the saliva, this may be acceptable.

Finally, there are many crucial factors to think about while developing the dissolution technique, and there are numerous possibilities available because there are no specified requirements or none. The approach selection should be well-founded and supported, nevertheless.[47] The Office of generic drug of the USFDA database also listed official recommended dissolution methods for oral, buccal, sublingual

**Drug content, assay content, and content uniformity**

Assay test will ensure the amount of the drug content delivered through the formulation to patient. The test that aids in understanding and maintaining the homogeneity of the medication content in the dosage form is the content uniformity test. Both tests can be evaluated using appropriate analytical technique using validated methods.Limit of assay is 90-110 % and Limit of content uniformity is 85–115%.[48]

**The remaining water content**

For each unique formulation, the residual water content of the films must be precisely determined because it may considerably affect any of the stated attributes. In order to prevent water transferences between the product and the surrounding room, it is also essential to monitor and regulate the room conditions throughout production (temperature and relative humidity). The mechanical properties of the polymeric matrix may be impacted by an excess or deficiency of water content. Water molecules may act as a plasticizer by interposing in polymer chains, hence the loss of water may be a factor in the development of brittle polymeric matrices. The polymeric matrix may then absorb too much water, leading to the formation of sticky films that could stick to the patient's fingers and/or the packaging.

**6.**Packaging techniques

Packing is one of the critical parts of the manufacturing of the oral films. Generally oral film are consider as moisture sensitive drug product and the film are packed as single unit pack and multiple pack depend upon the requirement of the drug product dosage regimen. [49]

**a. Unit dose – Peel pouch technique**

Unit pack is costly and more protective compared with multi dose pack. The unit pack can be opened at time of dose requirement. The unit packs are generally foil packed, plastic pouch and aluminum pouch.

Advantages:

Easy to handle and use

Moisture sensitive drug are packed in the unit dose.
Easy to design in required size, shape and can customized.

**b. Multi dose – Cassette packing technique.**

Multi dose packs are comparably low cost. The drug products which are less sensitive to moisture and used for more time in a day are packed as multi dose pack. The principal applications for this kind of strip packaging are products with multiple dosages, such breath fresheners and nutritional supplements. The consumer can keep a set of strips in a cassette and utilise them as needed at regular intervals.

Advantages:

- Easy to carry more strips.
- Low cost compared to unit pack
- Customized the packs depend upon the dosage regimen.
- After every strip is distributed, it is simple to open or close.
- A clever design limits the number of strips that can be supplied in an attempt.
- provision for attractively designed carton packing[50]

**7.Clinical trials and regulatory pathway**

A database of human participant clinical studies with public and commercial funding is kept by the National Institutes of Health in the United States.

From the database, clinicaltrials.gov, the studies which carried out on the Oral film, thin, film, buccal film and mucosal film are extracted and their studies details were mentioned in the **table 1.** [51,52,53]

**Table: 1 oral flim extraction and studies .**

| S. No | NCT No | Title | Conditions | Phase |
|---|---|---|---|---|
| 1 | NCT04206826 | Tolerance and Efficiency of an Intrabuccal Biological Film to Enhance Oral Dryness Sensation: The "PREDELFI" Clinical Pilot Study | •Sicca Syndrome<br>•Xerostomia | NA |
| 2 | NCT04300621 | A Study of Different Oral Thin Film (S)-Ketamine Formulations for Sublingual Administration in Healthy Participants | •Healthy | Phase 1 |
| 3 | NCT03996694 | Single Dose Crossover Study to Compare the Respiratory Drive After Administration of Belbuca, Oxycodone and Placebo. | •Respiratory Depression | Phase 1 |
| 4 | NCT03953820 | Diazepam Buccal Film (DBF) – Diastat Rectal Gel (DRG) Crossover Study | •Epilepsy | •Phase1<br>•Phase 2 |
| 5 | NCT03808259 | A Study to Investigate the Different Modes of (S) Ketamine Administration in Healthy Participants | •Healthy | Phase 1 |
| 6 | NCT03402503 | Safety, and Efficacy of a New Buccal Film of Montelukast in Patients With Mild to Moderate Alzheimer's Disease | •Alzheimer Disease | Phase 2 |
| 7 | NCT03510338 | Pharmacoscintigraphic Study to Evaluate Two Sildenafil Products | •Erectile Dysfunction | Phase 1 |
| 8 | NCT03679975 | Riluzole Oral Soluble Film (ROSF)Swallowing Safety in Amyotrophic Lateral Sclerosis (ALS) | •Amyotrophic Lateral Sclerosis | Phase 2 |
| 9 | NCT03457753 | Riluzole Oral Soluble Film Safety and Tolerability in Amyotrophic Lateral Sclerosis | •ALS | Phase 2 |
| 10 | NCT03428360 | Safety and Tolerability Study of Diazepam Buccal Soluble Film (DBSF) in Subjects With Epilepsy | •Epilepsy | Phase 3 |

| | | | | |
|---|---|---|---|---|
| 11 | NCT03428360 | Safety and Tolerability Study of Diazepam Buccal Soluble Film (DBSF) in Subjects with Epilepsy | •Epilepsy | Phase 3 |
| 12 | NCT03615820 | Niosomal Propolis as Oromucoadhesive Film: In-vitro, Ex-vivo & In-vivo Investigations | •Drug Effect<br>•Drug Effect Prolonged | Phase 1 |
| 13 | NCT03222349 | Assessment of Pharmacokinetics and Safety of Diazepam Buccal Soluble Film in Pediatric Patients | •Epilepsy | Phase 2 |
| 14 | NCT03179891 | Study of Diazepam Buccal Film Administered in the Interictal and in the Ictal-Periictal States to Adults with Epilepsy | •Epilepsy | Phase 2 |
| 15 | NCT02849093 | Optical Coherence Tomography of Ocular Structures in Epiphora and Dry Eye Syndrome. | •DryEye Syndrome<br>•Epiphora<br>•Sjögren's Syndrome | NA |
| 16 | NCT02501109 | Comparative Bioavailability Study of Aripiprazole 10 mg Oral Soluble Film vs Abilify® 10 mg Tablet in Healthy Volunteers | •Schizophrenia | Phase 1 |
| 17 | NCT02239770 | Pharmacokinetics of Nicotine Film in Smokers | •Smoking Cessation | NA |
| 18 | NCT03669263 | A Dose Titration Study of Fentanyl Buccal Soluble Film for Breakthrough Cancer Pain in Taiwan | •Breakthrough Cancer Pain | NA |
| 19 | NCT03070561 | Evaluating Peanut Immunotherapy Dissolving Film in Healthy Subjects | •Peanut Allergy<br>•Immunotherapy<br>•Pharmacokinetics | Phase 1 |
| 20 | NCT02453503 | Comparison of Triamcinolone Acetonide Mucoadhesive Film and Licorice Mucoadhesive Film Effect on Lichen Planus | •Oral Lichen Planus | Phase 2 |
| 21 | NCT01871285 | Evaluation of the Tolerability of SwitchingSubjects on Chronic ATC Opioid | •Pain | Phase 2 |

| | | | | |
|---|---|---|---|---|
| | | Therapyto Buprenorphine HCl Buccal Film | | |
| 22 | NCT02075749 | Comparing Triamcinolone Acetonide Mucoadhesive Films With Licorice Mucoadhesive Films | •Mucositis | Phase 1<br>Phase 2 |
| 23 | NCT01844648 | Study of the Safety and Efficacy of Tropicamide Thin Films to Reduce Hypersalivation in Parkinson's Patients | •Sialorrhea (Excessive Drooling) | Phase 2 |
| 24 | NCT01676844 | Investigating a New Way of Giving Medicine to Newborn and Preterm Babies | Hypophosphatasemia Osteopenia of Prematurity | phase 2 |
| 25 | NCT01755546 | Long-term Open-Label Safety Study to Evaluate EN3409 | •Low Back Pain<br>•Osteoarthritis<br>•Neuropathic Pain | Phase 3 |
| 26 | NCT01675167 | Efficacy Study to Evaluate BuprenorphineHCl Buccal Film in Opioid-Experienced Subjects | •Low Back Pain | Phase 3 |
| 27 | NCT01702532 | Nicotine Mouth Film for Craving Relief. | •Smoking Cessation | Phase 3 |
| 28 | NCT01633944 | Efficacy Study to Evaluate BuprenorphineHCl Buccal Film in Opioid-Naive Subjects | •Low Back Pain | Phase 3 |
| 29 | NCT01431742 | Long term Safety Study of BEMA Buprenorphine in Subjects With Chronic Low Back Pain | •Pain<br>•Low Back Pain | Phase 3 |
| 30 | NCT01298765 | Long term Safety Study of BEMA Buprenorphine in Subjects With Chronic Pain | •Pain & Low Back Pain, Osteoarthritis<br>•Neuropathic Pain | Phase 3 |
| 31 | NCT01256450 | Efficacy and Safety Study of Buprenorphine HCl Buccal Film in Subjects With Low Back Pain | •Pain<br>•Low Back Pain | Phase 3 |

| | | | | |
|---|---|---|---|---|
| 32 | NCT01167504 | Factors Controlling the Formation of Salivary Films | •Healthy | Phase 2 |
| 33 | NCT00941304 | Study of Buprenorphine HCl Buccal Film in the Treatment of Dental Pain | •Dental Pain | Phase 2 |
| 34 | NCT01217190 | Crossover Study Comparing Ondansetron Orally Dissolving Film Strip (ODFS) With Zofran Orally Disintegrating Tablets | •Nausea and Vomiting, Postoperative | •Phase 1<br>•Phase 2 |
| 35 | NCT00696137 | Long-term Extension Study of BEMA™ Fentanyl | •Respiratory Depression | Phase 3 |
| 36 | NCT00761137 | Safety and Efficacy Study of NH004Films for Relief of Sialorrhea Symptoms in Parkinson's Disease Patients | •Sialorrhea Secondary to Parkinson's Disease | Phase 2 |
| 37 | NCT00640835 | Safety and Tolerability of Buprenorphine/Naloxone Film Strips | •Opioid-Related Disorders | Phase 2 |

If we chose the Abbreviated New Drug Application approach for the US FDA's product approval process, the product must be bioequivalent to the drug's current oral product. In this, therapeutic equivalence (bioequivalence study in which the 90% confidence interval of the log transformed ratio of Test and Reference product pharmacokinetic parameters AUC0-t, AUC0-inf, and Cmax should be within the acceptable limits of 80% to 125%) and in-vitro dissolution studies are included. This generic approval procedure (as described in section 505(j) of the Food, Drug, and Cosmetic Act) is not accompanied by any clinical investigations.

Oral strip products could have a different target PK profile than currently on the market products. As a "new dosage form," the Oral Strips product requires approval in accordance with section 505(b)(2). A fresh clinical investigation would be necessary in this situation. The benefit of the current clinical research is that it would grant the product three years of marketing exclusivity. If the chemical is the same as the one in the approved product, preclinical toxicity studies are not necessary. These trials are intended to demonstrate the features of safety, tolerability, and efficacy. Testing for oral mucosa irritation is done on both human volunteers and animal models. According to EMEA regulations, acceptance of a marketing authorization is important in Europe. Either of the two approaches, namely the mutual recognition process or the decentralisation technique, can frequently be used.

**8.Oral films available in market**

The final innovative medication approved by the US Food and Drug Administration (FDA) in 2020 is KYNMOBI (Apomorphine hydrochloride) 10mg, 15mg, 20mg, 25mg and 30mg sublingual film dosage form is approved by USFDA on 21 may 2020 with prescription marketing statusfor SUNOVION PHARMAS INC. BELBUCA (Buprenorphine hydrochloride) 0.075mg, 0.15mg, 0.45mg, 0.6mg, 0.9mg base buccal films with prescription marketing status and The last two products approved by the FDA under the 505(b)(2) path were Belbuca® for chronic pain and Bunavail® for opioid addiction. A list of drug approved in USFDA was captured in **Table 2** [54,55,56]

**Table: 2 list of the approved prescription drug in USFDA and their status.**

| Product Name | Active ingredients | Market status | Dosage form |
|---|---|---|---|
| KYNMOBI | Apomorphine Hydrochloride | Prescription | Sublingual film |
| BELBUCA | Buprenorphine Hydrochloride | Prescription | Buccal film |
| SUBOXONE | Buprenorphine Hydrochloride; Naloxone Hydrochloride | Prescription | Sublingual film |
| SYMPAZAN | Clobazam | Prescription | Oral film |
| ZUPLENZ | Ondansetron | Prescription | Oral film |

| | | | |
|---|---|---|---|
| EXSERVAN | Riluzole | Prescription | Oral film |
| BUNAVAIL | Buprenorphine Hydrochloride; Naloxone Hydrochloride | Discontinued | Buccal film |
| CASSIPA | Buprenorphine Hydrochloride; Naloxone Hydrochloride | Discontinued | Sublingual film |
| ONSOLIS | Fentanyl citrate | Discontinued | Buccal film |
| NEXCEDE | Ketoprofen | Discontinued | Oral film |

**14. Conclusion**

Oral film technology is an emerging novel approach for drug delivery system. Considering the technology is patient friendly towards all age group of peoples especially in pediatrics and geriatrics population. It may open up new possibilities for manufacturers to enhance the current drug product's life cycle management. This can enhance the drug's quick beginning of action, help it avoid first-pass metabolism, and increase its bioavailability. Technology for oral films can be used for more than just quick drug administration. it can also extended for the sustained drug delivery as buccal patches, mucoadhesive drug delivery, gastro retentive drug delivery system and sublingual delivery choices. Oral film technology also serves as platform to tailored drug delivery based on the patient requirements and meet the unmet needs of the other delivery system. Regulatory acceptance of oral film drug products demonstrates optimistic scopes to develop the drug products in the pipe line of oral film technology. The global oral film market predicted to surpass 4068.7 million USD at 2023 and this gives a solid opportunity in the global market to reach the technology. [56] This oral film technology platform gives break through on the business future for the pharmaceutical, nutraceutical and cosmeceutical products.

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