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Fast Dissolving Thin Film: A Novel and Compliant Dosage Form for Patients

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ABSTRACT

In pharmaceutical research, a new age of science and technology focuses on oral medication delivery. Tablets and capsules have limited bioavailability, frequent use, adverse effects, and patient noncompliance. By creating unique medication delivery mechanisms, researchers avoided established systems. In paediatrics and geriatrics, fast-dissolving medication delivery devices are popular. Orally disintegrating films are better than fast-dissolving pills, which might suffocate. Because they circumvent disintegration and the first pass impact following oral administration, they're popular.

The oral fast-dissolving film is a revolutionary, enhanced delivery technology. This dosage form is gaining popularity because to its cost-benefit, quick dissolving without water, and compliance with elderly and pediatric patients in emergency situations and certain disorders. Also, it's a good dose form for drugs with pre-systemic metabolism and low bioavailability. Recently, quick dissolving films have become a popular alternative to tablets. The films disintegrate over a moist surface, such as the tongue, within seconds, so the user may ingest the medication without extra liquid. Convenience boosts marketing and patient compliance. As the medicine is immediately taken into systemic circulation, degradation and first pass effect are avoided. These factors make this formulation popular and acceptable among pediatric, geriatric, and choking patients. Over-the-counter pain and motion sickness films are sold in the US. Thin film formats are developed using transdermal medication delivery technology. This review article discusses the history, benefits, drawbacks, limits, ideal qualities, classification, formulation, method of manufacture, in-vitro and in-vivo quality metrics, technological advancements, commercial trends, and past work on oral rapid dissolving films. It's one of the fastest-growing dosage forms due to its unique properties, innovative attributes, competitive position, and cost-adequacy.

Keywords: Fast dissolving film, oral formulation, novel, first pass metabolism, patient compliance

Introduction

Patients tend to choose oral dosing over other delivery methods. Oral drug delivery research has led to the creation of new dosage forms, including fast-dissolving oral thin films and fast-disintegrating versions of traditional tablets and capsules (OTF).

As an alternative to traditional dosage forms, fast dissolving drug delivery methods were initially developed in the late 1970s. "a solid dosage form containing therapeutic chemicals that disintegrates fast, generally within a couple of seconds when put onto the tongue," is how the Centre for Drug Evaluation and Research

(CDER) describes ODTs. U.S. Food and Drug Administration (FDA) guidelines define OTFs as "a thin, flexible, non-friable polymeric film strip containing one or more dispersed active pharmaceutical ingredients that is intended to be placed on the tongue for rapid disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract" [1]. Pharmaceutical OTFs are maturing into established market niches. In 2010, Zuplenz (Ondansetron hydrochloride- 4 mg, 8 mg) became the first OTF available via prescription. Quickly after that, Suboxone was given a second green light (Buprenorphine and Naloxone). According to the data, 80% of patients would rather take a pill that dissolves in their mouth than a pill that stays in their mouth [2]. These characteristics, together with the benefits of convenience and compliance, have been (and will continue to be) the driving force behind the expansion of ODT and OTF pharmaceuticals. Designed to dissolve quickly in the mouth, oral thin films are supplied as a flat sheet directly into the mouth. This is a helpful dose form since the drug's effects may be felt very instantly upon contact with the oral mucosa. According to the European Pharmacopoeia, these tablets are "orodisperse" since they are meant to be dispersed quickly in the mouth before being swallowed. Fast dissolving films are a well-proven and well approved technique for the systemic medication administration of active pharmaceutical ingredients (API) [3].

Oral thin films are produced as a large sheet, which is then sliced into smaller pieces that make up a single dose unit before being packaged. When a quick, targeted effect is needed in the mouth, such when treating a toothache, an oral ulcer, a cold sore, or teething, a thin film may be placed directly within the mouth. You may put just about any medicine in this dose form, including those for coughing, asthma, allergies, ED, sore throat, GI issues, nausea, pain, and the central nervous system. Oral thin films may also be used to make coffee strips, multivitamins, sleeping pills, snoring remedies, etc. [4].

History of film formulation

Researchers nowadays always seek for new approaches to creating cutting-edge, modern dosage designs that are not only foolproof and highly effective, but also economical and straightforward to create. Patient-friendly dosage forms are in high demand. Medicines that may be taken by mouth are generally regarded as the best and most sought after among the several common dose types [5]. While the introduction of oral quick dissolving tablets in the 19th century was a step in the right direction toward addressing the problems associated with liquid formulations, the drawbacks of the tablet form paved the way for the development of an entirely new technology: mouth dissolving films. Though rapid dissolving oral films have been in the spotlight recently, the vast majority of fast-dissolving pharmaceutical medications come in tablet form and dissolve within minutes. Fast-dissolving films placed on the tongue dissolve instantly without the need for water or chewing. Figure 1 depicts the original concept for this ground-breaking medication delivery system, which was developed in the 1970s.

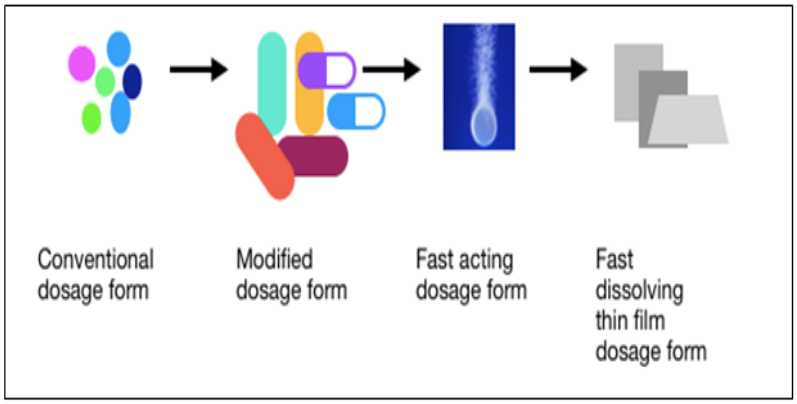

Figure 1 Progress in Oral Dosage Form

Merits

- Several benefits set oral quick dissolving thin films apart from other oral preparations
- Large areas of exposed surface aid in both disintegration and breakdown [7].
- Unlike orodispersible tablets, rapid dissolving thin films do not need special packaging and may be stored and transported with ease. Each film strip assures accurate dose administration[9] [10].
- The drug-containing film rapidly dissolves in the mouth, and it doesn't even need to be mixed with water before administration [11].
- Any special practice of administration is not required in the case of oral thin films [12].
- The dosage form provides the best systemic absorption to drugs that experience the first effect [13], hence improve their bioavailability [14] therefore in this way promotes rapid therapeutic action [15].
- Due to the escape of first-pass metabolism, this delivery system can reduce dose and side effects [16].
- This dosage form is extremely patient compliant as it is non-invasive [17,18], suitable for paediatrics and geriatrics [19]uncooperative and unconscious patients with different illnesses [20], for cardiovascular patients, for people with respiratory ailments and chemotherapy patients, patients having swallowing problems [21]
- It is exceptionally useful in cases where a local action and an ultra-rapid drug onset are needed [22].
- It delivers a pleasant mouthfeel and also valued for masking the taste, moreover, well favourable for travelling patients [23].
- The oral bioavailability of drugs also gets enhanced in this dosage form because of lesser drug decomposition. [24]
- Fast dissolving oral thin film has longer and improvised stability. It has the advantage of both the solid and liquid dosage forms concerning solubility and bioavailability respectively. The unique packaging of OFDTF enhances product stability.
- There is an immediate release of one or more drug ingredients, as these films disintegrate within seconds once taken orally [25].
- The dosage form is technically advantageous since its excipients include sugars and belong to the GRAS category [25]
- Business benefits concerning product differentiation and promotion, as well as patent extension, are also provided. An unprecedented business structure is not required for industry [26]

Clinical Advantages [27, 28, 29]

- As oral thin films are given by oral route their administration is easy as it employs the oral route.
- In paediatric and geriatric patients the risk of choking or suffocation is reduced.
- Oral Thin Films are a better alternative for patients with nausea.
- Oral Thin Films do not required to be swallowed with water.

Market Advantages [30]

- This novel drug delivery system presents pharmaceutical companies with patents on the verge of expiration to increase the revenue cycles.
- OTFs dissuade the misuse, tampering and abuse related to some prescribed drugs because the film is loaded with an exact amount of drug.
- The oral thin films market is currently in its embryonic stages and limited only to certain over the counter drugs available within the American, Japanese and EU Markets. Thus, researches and corporations have a great scope in formulating drugs that haven't been previously formulated into OTFs and developing newer and cheaper technologies.
- In India, per Indian demographics for 2017 roughly 13.39% of the population is senior citizens while 45.7% are children. Thus, Indian investors have a good consumer range and this technology is inchoate in our country

Demerits [31,32]

- Special moisture-resistant packaging is required as fast dissolving thin films are sensitive to moisture, and this particular packing is costly.
- From the technical aspect, dose uniformity in the strip is a serious risk.
- A significant manufacturing difficulty that confronts manufactures is that the drying time required for the OTFs. Since thermolabile drugs prohibit the utilization of hot air ovens and high temperatures, it takes each day for the films to dry at room temperature thereby reducing the production rate.
- As the films are highly hygroscopic and tend to lose stability in environments having high relative humidity.
- Drugs which are unstable at the buccal pH or irritate the mouth mucosa cannot be formulated into thin films.
- The co-administration of multiple drugs remains to be a challenge because the dissolution time is affected.
- Drug with small dose requirement can only be administered.
- Taste masking is required for bitter taste drugs.
- Special packaging is required for OTFs, so as to protect it from water.

Limitations [33]

- Drugs with unpleasant taste must be avoided or inert substances needed to mask the taste of bitter API.
- There is a limitation in administration or incorporation of higher doses.
- Mucosal irritants shouldn't be administered following this route.
- Saliva contains a proteolytic enzyme, inhibition of which is required in case of protein-based drugs, with the help of enzyme inhibitors.

Absolute characteristics

- Fast dissolving films must possess the following properties: [34]
- Adequate taste/ must not be bitter
- A pleasant sensation in the mouth.
- Having lesser friability and appropriate mechanical capacity to combat post-production handling.
- Good stability in natural conditions.
- The drug must not have a higher dose.
- No or minimum residue should be left in the mouth
- It should dissolve rapidly and release drug content instantly in the oral cavity.
- It should possess compatibility with other ingredients
- The drugs having smaller or moderate molecular weight are preferred.

- The drugs having better stability and solubility in water & saliva are selected.
- It should not completely ionize at the pH of oral cavity.
- The drugs should permeate through the oral mucosal membrane.

It's no surprise that thin-film dosage forms of pharmaceuticals are so popular, given their convenience and efficiency. Both well-established pharmaceutical firms and start-ups are interested in this technology. Sales have surpassed significant milestones in both the United States and Europe. In 2007, the market for pharmaceutical items in oral thin-film formulations was valued at $500 million. By 2010, this figure was projected to rise to $2 billion. Furthermore, a study projects that the worldwide market for thin-film pharmaceutical products would grow from $7.1 billion in 2015 to $15.9 billion by the end of 2024. Consequently, a rise of 117% is predicted during the next decade (see **Figure 2**) [35].

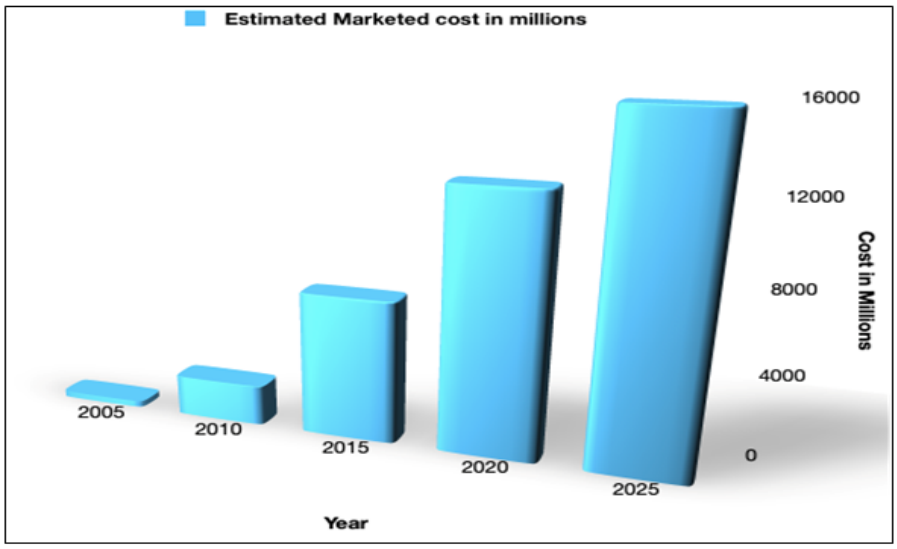

Figure 2: Estimated Marketed Values of Thin Film

Classification

Figure 3 displays a classification system for fast dissolving thin films based on their individual characteristics [36].

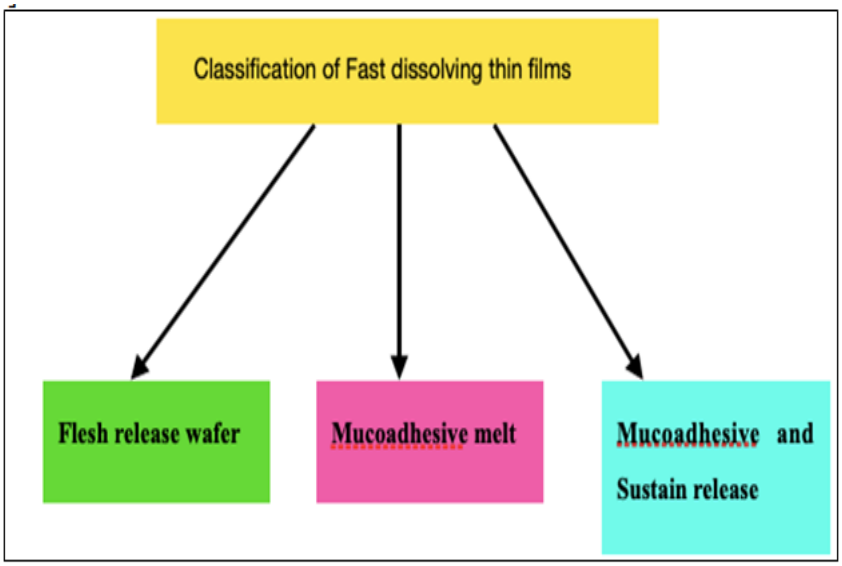

Figure 3: Classification of Fast Dissolving Thin Film

Flesh release wafer: The flesh release wafer has dimensions of around 2-8 cm2 in size and 20-7 µm in thickness. It has a solid solution as the drug phase and is composed of highly soluble hydrophilic polymers in a single layer. The strip dissolves in less than a minute over the tongue, delivering either local or systemic effect [37].

Mucoadhesive melt – away wafer: The thickness of a mucoadhesive melt away wafer is between 50 and 500 µm, and the area is between 2 and 7 cm2. Suspended drug particles or a solid solution may be used as the drug phase in either a monolayer or multilayer system. Hydrophilic, water-soluble polymers are employed. When the strip is put in the mouth, it quickly turns into a gel after being dissolved. The place of action may be regional or global [38].

Mucoadhesive and sustain release: About 2–4 cm2 in size and 50–250 µm in thickness characterize a mucoadhesive and sustained release film. There are many layers to this system, all of which are made up of polymers that are either insoluble or just slightly soluble in water. A drug's form might range from solid solution to solid suspension. Depending on whether it is placed over the buccal or gingival area, the strip has either systemic or local action, and dissolves in 8-10 hours at the most [39].

Formulation consideration

As the name implies, fast dissolving film is designed to dissolve in the mouth quickly and without the need of water, thus its creation requires extra care and attention. It has to have a certain look, flavor, and texture in your tongue. Consist mostly of the elements listed below.

Selection of API

The typical drug concentration in the film formulation is between 5% and 30% weight-per-weight. Small dosages of drugs that are stable and can pass through the oral mucosa easily are excellent for use in mouth dissolving films [40].

Selection of excipients

Generally Recognized as Safe (GRAS-listed) and accepted excipients are used in the formulation of orodispersible films.

Polymers

When it comes to creating thin films, there is a wide variety of synthetic and natural polymers from which to choose. Because of their lower toxicity and higher accessibility, fast-dissolving films produced from natural polymers like mucilages and gums are becoming attractive. It's the most important factor and shouldn't be lower than 45 percent by weight of the whole dry film. While the oral film's ingredient list does include polymers, active pharmaceutical fixing, film offsetting administrators, sugars, flavors, colors, salivation strengthening experts,

added substances, surfactants, etc., the polymer is the first and, by far, the most fundamental fixing which aids in film development. In order to have ready quickly dissolving mouth films, a wide range of polymers is available. Oral films that make use of film framing polymers have attracted a lot of interest in medical and nutritional contexts. One of the most important and fundamental elements for effectively enhancing film formation is the determination of polymer. Each polymer may be used alone or as part of a mixture to achieve the desired film characteristics. Using hydrophilic polymers, a thin film may be prepared for oral fast-dissolving film, which rapidly dissolves when placed on the tongue or buccal cavity. It is recommended that at least 45%w/w of polymer be supplied based on a total load of the dry film, since the strip framing polymer (which forms the foundation for the FDF) is the most fundamental and important portion of the FDF [42].

Oral film preparation necessitates the use of polymers that are safe for human consumption, won't irritate the mucosa, won't cause secondary infections in the oral mucosa or teeth, are free of leachable impurities, won't slow the film's disintegration time, are tasteless, have good wetting and spreadability properties, exhibit sufficient peel, shear, and tensile strength, are easily accessible, cheap, and have a long shelf life Because of their potential biocompatibility, hydrophilic polymers are receiving increasing interest for use in healthcare and the pharmaceutical industry. They're malleable from the molecular to the technological level, allowing for individualized design. Hydrophilic polymers have found important uses in the medical industry [43].

These days, quick mouth dissolving film may be made using either natural or synthetic polymers.

Classification of polymers used for Mouth dissolving film

Natural polymers are preferable for medicinal uses because they are effective, readily available, and non-hazardous, however synthetic polymers may also be used. It's possible to biodegrade them, they're suitable for medicinal changes, and, barring rare circumstances, they're also biocompatible. Some of the biopolymers employed in these slow-release pharmaceuticals are made from plants. Plant-derived substances provide a number of possible challenges, including, for example, being blended in minute quantities and in mixes that are confusing, which may change as per the location of the plants just as other elements, such as the season, may affect them. Because of this, a separation and cleaning procedure may become necessary, which may be somewhat expensive. The protection of one's intellectual property is another matter of growing importance [44].

Importance of Herbal Polymers over Synthetic Polymers is-

They are cheap, readily accessible, non-hazardous, biocompatible with human cells, and non-toxic.

Therefore, natural polymers are currently chosen over synthetic polymers as a result of the aforementioned benefits.

Classification of Natural Polymers

The purpose of this review is to examine the research and reviews conducted over the last decade with regards to the natural polymers utilized for quick mouth dissolving films.

Fast dissolving oral film is made using a variety of polymers. In this section, we'll go through the physicochemical characteristics and film-forming abilities of a few of them [45].

1. Pullulan:

The primary structure is a linear -glucan, which is made up of three glucose units linked together in α-(1, 4) fashion in maltotriose units linked together in α-(1, 6). Maltotriose has α-(1, 4) glycosidic link between its three glucose units, and α-(1, 6) glycosidic bond between its two adjacent maltotriose units. The additional flexibility and enhanced dissolvability that result from the normal rotation of (1 → 4) and (1 → 6) bonds are apparent. In addition to adhesive qualities and the capacity to shape into fibers, compression moldings, and robust, oxygen-impermeable coatings, pullulan is endowed with unique physical features thanks

to its novel linking pattern. The adaptability [46] is due to the α-(1, 6)connections between the repurposed maltotriose units throughout the chain.

2. Gelatin:

Gelatin is formed from collagen extracted from animal skin, bone, and fish skins and then heated to denature the protein. Gelatin is the common name for a mixture of filtered protein fractions obtained from the acid hydrolysis (type A gelatin) or alkaline hydrolysis (type B gelatin) of animal collagen. Linear polymers formed from amino acids bonded together by amide bonds make up the bulk of proteins [47].

The increased amino acid content of mammalian gelatins is primarily responsible for their superior physical qualities and thermal stability compared to those of fish gelatins. Mammalian gelatin is used to create an appetizing film or coating.

3. Sodium Alginate:

To put it simply, alginate is not a food. Sodium alginate is mostly composed of the sodium salt of alginic corrosive, which is a polychronic acid mixture derived from D- mannuronic acid and L-guluronic acid deposits.

Solid films created from alginate are both edible and hydrophilic, so they easily absorb water. The mechanical characteristics of edible film may be enhanced by blending starch and alginate [48].

4. Pectin:

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Solid films created from alginate are both edible and hydrophilic, so they easily absorb water. The mechanical characteristics of edible film may be enhanced by blending starch and alginate [48].

5. Rosin:

Rosin, an acidic thermoplastic, is a material with unique properties. Hydrophobic and biodegradable best describe this biomaterial. The acid in resin is its primary component. Originating in the ancient Ionic city of Colophon, rosin is also known by the names colophonia resina and colophony.

The plasticizer-free solutions yielded translucent, brittle films that were easy to work with. Plasticizers have a significant role in the presentation of film coating, resulting in decreased tensile strength and increased elongation and flexibility of the films [50].

6. Starch:

Starch is a biopolymer composed of glucose units and divided into the two main components, amylose and amylopectin. Amylose concentration in starch granules ranges from around 16 percent to about 28 percent, depending on the source of the starch; waxy starch, on the other hand, contains just amylopectin. There are three main crystalline allomorphs of starch found in nature; we'll call them A, B, and V. Starch films high in amylose crystallize into B-type structures rapidly, whereas starch films high in amylopectin crystallize into B-type structures over time. The starch's amylose is to blame for its film-forming properties [51].

In lieu of polymeric polymer, starch may be used extensively or entirely. These films are flavorless, tasteless, and colorless in addition to being transparent or translucent.

Films made from high-amylose maize starch or potato starch were remarkably stable over time, retaining much or all of their initial elongation while either maintaining or showing a minor increase in tensile strength [52].

7. Maltodextrin:

Maltodextrin may be absorbed and stored as rapidly as glucose, demonstrating its high digestibility. Maltodextrin is usually a combination of chains ranging in length from three to seventeen glucose units [53].

8. Chitosan:

Derived mostly from crab shells, chitosan (β-(1, 4) - 2-amino-2-deoxy-D-glucopyranose) is the second most common non-toxic polymer in nature after cellulose [54].

9. Gum Carrageenan:

In its purest form, carrageenan is a long, straight chain of partly sulfated galactans.

Extractions of sulphated polysaccharides from the cell walls of several red seaweeds (Rhodophyceae). Carrageenans come in a wide range of forms and are produced by different types of seaweed. Most recently, carrageenan films have been regarded as less hazy than starch-based films [55].

Plasticizer

As a key component, the plasticizer gives the mouth dissolving film its pliability and makes it less prone to breaking as it dissolves in the mouth. The glass transition temperature is reduced, and the polymer's strength is increased. Since concentrations of plasticizers above 30% cause drying problems and concentrations below 10% render the product less flexible, a middle ground of 20% is used [56].

Sweeting agent

Dissolving formulations rely heavily on sweeteners to improve consumer acceptance. Natural and artificial sweeteners are both acceptable in a 3-6% w/w concentration [57], where they can be used singly or in a blend.

Natural sweeteners include things like fructose, glucose, honey, mannitol, sorbitol, liquorice, and glycerol sucrose, whereas artificial sweeteners may or may not have nutritional value.

Maltose, fructose, and glucose are examples of nutritive sweeteners; polyols like mannitol, sorbitol, maltitol, srythriol, and xylitol are examples of artificial sweeteners. Novel sweeteners include trehalose and tagatose, and non-nutritive sweeteners include sucralose, saccharine, neotame, and aspartame [58].

Saliva stimulants

Faster film dissolving may be achieved with the use of saliva stimulants. Saliva stimulating substances include things like citric acid, ascorbic acid, lactic acid, and tartaric acid, however citric acid is the best option. These stimulants are employed in mixtures or as single agents at a concentration of 2-6% w/w [59].

Colouring agent

Dissolving thin films in the mouth are produced using dyes that have been FDA and C approved. One such material is titanium oxide. Use no more than 1% w/w [60] of the solution.

Stabilizing and thickening agent

When used in preparation for casting, stabilizing and thickening agents increase the viscosity of dispersions. Use a concentration of roughly 5% w/w. In most cases, thickeners and stabilizers are added in the form of emulsifiers, surface active agents, or gums. Commonly used gums include carrageenan, xanthan gum, locust bean gum, and cellulose derivatives [61].

Flavouring agent

Flavor preferences vary from person to person based on factors such as age, culture, and, most significantly, formulation. Flavoring agents include oleoresins, synthetic flavor oil, and selected plant extracts. Mint flavor, fruity flavor, and confectionery flavor are just few of the many flavoring agents that may be used into a composition. Flavoring agents, together with cooling agents to improve tongue feel, may be added to the formulation at concentrations of up to 10%, w/w [62].

Permeation enhancer

These permeability boosters help get more of the medicine into the body. Most often used permeation enhancers are menthol, dextran sulfate, benzalkonium chloride, Apoprotin, sodium taurodexycholate, cyclodextrin, cetylpyridinium chloride, Lauryl ether, azone, and sodium glycodeoxycholate [63].

Manufacturing Methods

The following procedures are often employed in the production of fast-dissolving oral films:

1. Solvent casting method
2. Hot melt extrusion
3. Semi-solid casting
4. Rolling method
5. Solid dispersion extrusion

Solvent casting method

In order to create oral thin films, the solvent casting approach is now used. Here, the plasticizer and the water-soluble polymer are combined in a distilled water solution. An electric magnetic stirrer is used to vigorously mix the solution for two hours before it is set aside to release any remaining air bubbles. After 30 minutes of vigorous stirring, the API and excipients have been completely dissolved and are ready to be combined. The last step is to cast the solution onto a surface that can accept the film's final shape. After the film has cured, it is peeled off. Buprenorphine hydrochloride sublingual films with abuse deterrents and microemulsion delivery for breakthrough pain control were also manufactured using the same solvent casting method. [64]

Hot melt extrusion

Granules, extended-release pills, transdermal, and transmucosal drug delivery systems may all be prepared using this technology. When it comes to film processing, this methodology uses heat to mold polymers into movies instead of the more conventional solvent casting method. Hot melt extrusion machinery includes an extruder, as well as downstream auxiliary equipment and inspection instruments. Each extruder has a feeding hopper barrel, screw, die, screw-driving machine, and heating/cooling device. Film casting utilizing aqueous or organic solvents is used to create thin films for transdermal/transmucosal medication administration and wound treatment. [65]

Polymer that cannot be dissolved in water is employed in this process. Prepare an ammonia and sodium hydroxide solution of the insoluble polymer. A gel-like solution is created by combining the two solutions with the right quantity of plasticizer. Thin films or ribbons are created by spreading this gel-like fluid over thermoregulated drums. The ratio of acid-insoluble polymer to film-forming polymer is kept at 1:4. Many acid-insoluble polymers exist, such as cellulose acetate phthalate, cellulose acetate butyrate, etc. [66].

Rolling Method

The medication is rolled together with solvents and a carrier in this procedure. A film-forming polymer solution or suspension is made and then rolled. Rheological factors must be taken into account while designing the solution or suspension. Water and water-and-alcohol mixtures are the primary solvents in this technique. Processed in a high shear processor, active pharmaceutical ingredients (API) and other excipients are dissolved in a somewhat watery medium. Hydrocolloids that can be dissolved in water create a silky, viscous liquid when mixed with water. The resultant suspension or solution is then utilized to roll out the film [67].

A second metering pump is used to inject a measured quantity of solution into the pan. Film thickness was calculated via a measuring roller. Once the film has been produced on the substrate, the transport roller will take it away. Bottom drying is managed to remove moisture from the wet film. When the film is ready, it is sized and shaped as needed [68].

Solid dispersion extrusion

Amorphous hydrophilic polymers in solid form are involved in the process of dispersing two or more active compounds in an inert carrier. The active pharmaceutical ingredient (API) is first dissolved in an appropriate liquid solvent before being added to a PEG melt at temperatures below 70 degrees Celsius. Unfortunately, the chosen solvent or medication was incompatible with PEG's molten state. Following this, dies are used to cut the solid dispersion into films of the desired thickness and form [69].

Advancement in oral thin film technologies

Printing technologies

Production of polymeric thin films may benefit from cutting-edge techniques like 3D printing. It has the potential to serve as a mechanism for manufacturing the dose forms that each patient needs. This may be useful in the development of personalized medicine. Printing technology is on the rise due of its adaptability and low price. 8 Off-the-shelf consumer inkjet printers may be used to deposit inks filled with drugs, resulting in precisely dosed units of active pharmaceutical components. Flexographic printing was utilized to cover the drug-loaded substrate with a polymeric thin film [70], while inkjet printing was used to print the active

pharmaceutical component on a variety of substrates.

All of the different methods of printing help to making films with more consistent dosing and distribution of the medicine throughout the film. As a conclusion, printing a medicine on dosage form is the most recent intervention for film production, and it has proven an effective instrument for producing dosage forms with high levels of consistency, speed, and stability [71].

XGelTM film offers special advantages for healthcare and pharmaceutical industries. Vegans and vegetarians may rest assured knowing that no animals were harmed in the making of this product. Because of its GMO-free status and its ability to be processed in a continuous fashion, this film may be made at a reasonable price in a market where competition is fierce. XGelTM films have the potential to incorporate active pharmacological compounds in addition to providing taste masking, coloring, layering, and enteric properties. Because of this need, XGelTM film systems are widely utilized to encapsulate any oral dosing form. Water-soluble polymers that are specific to the task at hand make up the XGelTM film [72].

Soluleaves

Incorporating active substances, colors, and flavors into oral administration films is made possible with the use of this technology. The active chemicals and flavors in Soluleaves TM films are intended to dissolve fast in the mouth upon contact with saliva. When it comes to pharmaceuticals, this delivery system is ideal for younger or older individuals who may have trouble swallowing larger pills. Nutritional supplements and medicines for the treatment of coughs, colds, and stomachaches are among the many common uses for these delivery systems. Also, the active ingredient may be released gradually over the course of 15 minutes from films manufactured using the SoluleavesTM technology [73].

Wafertab

Ingestable filmstrips called WafertabTM may be used as a medication delivery device. The method enables for rapid degradation and actives release when the strip comes into contact with saliva in the mouth. Flavored versions of the WafertabTM filmstrip are often used to enhance their effectiveness in hiding unpleasant tastes. Careful dosing and incorporation into the XGelTM film's body prevents the active component from being exposed to excess heat or moisture, which may increase the film's long-term durability. WafertabTM may be made in a number of different sizes and forms, making them ideal for administering medications to individuals with swallowing difficulties. [74]

Foamburst

Similar to SoluleavesTM technology, but with the addition of a noble gas pumped into the film during production. This creates a honeycombed layer that evaporates fast and leaves the tongue with a novel sensation. Food and candy producers are interested in FoamburstTM because it may be used to transport and gradually release flavors [75].

Review of Oral Thin Films

Thickness

The thickness of the film may be measured using either a micrometer screw gauge or a calibrated digital vernier calliper. The optimal film thickness is between 5 and 200 m. Uniformity in film thickness is crucial as it is directly connected to the precision of dose distribution in the film [76]. The thickness of the film should be evaluated from five different locations (four corners and one in the centre).

Dryness test/Tack test

There are eight distinct stages of film drying: 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. Most of the research may be carefully adapted to evaluate pharmaceutical OTF, even though the procedures were developed to evaluate paint films. Tack refers to the strip's tensile strength and how well it adheres to an accessory (in this case, a piece of paper) that has been pushed against it.

Tensile strength

Tensile strength is defined as the tension at which a strip specimen breaks. As demonstrated in [78], it is calculated by dividing the load at rupture by the film's cross-sectional area.

Tensile strength = Load at failure × 100 / Film thickness × film width

Percent elongation

Strain is the result of applying force to a thin film (2 2 cm2) sample, which causes it to expand. When a strip is subjected to stress, it deforms, a process known as strain. It is evaluated with the use of the Hounsfield universal testing machine. In general, as plasticizer concentrations grow, so does the elongation of strips. The formula for this is [79].

$\%\ Elongation = Increase\ in\ length\ of\ strip \times 100 / Initial\ length\ of\ strip$

Young's modulus

The stiffness of a strip may be measured by its Young's modulus, also known as its elastic modulus. For elastic deformation, it is written as the stress-to-strain ratio:

Young′s modulus = Slope × 100 / Film thickness × cross − head speed

High tensile strength and Young's modulus are seen in rigid, brittle strips with little elongation. Film typically has a young's modulus of 0.30 0.07 Mpa.

Tear resistance

There are several factors that contribute to a material's final rupture resistance, including its rip resistance. One newton (or one pound of force) is the maximum stress or force required to shred the specimen (which is usually determined around the commencement of tearing). Folding endurance is tested when the load is applied at a relatively slow rate of 51 mm/min [80].

A film strip is cut and folded repeatedly at the same point until it breaks to determine the folding endurance. The number of times a film can be folded at the same spot without cracking is used to calculate the value of its folding endurance. Film typically has a folding endurance of between 100 and 150.

Index of edema

Testing of the film's swelling index is done using salivary fluid simulation. A sample of the film is weighed and then put in a stainless-steel wire sieve with the same mass. The mesh holding the film is placed into a mortar and filled with 50 cc of saliva substitute. The film's weight is monitored at regular intervals until it stabilizes at a constant value. The degree of swelling may be calculated using the following formula: [81]

SI = wt − wo / wo

Where,

SI=swelling index

Wt = the film's weight at time "t" and Wo = weight of the film at t = 0

The pH of the Surrounding Surface

It is vital to evaluate the pH of the film since the surface pH of a fast-dissolving strip might have detrimental effects on the oral mucosa. It's recommended that the surface pH of the film be around 7. This may be done using a pH electrode that measures both acids and bases. The pH of OTF was measured by putting an electrode on the film after it was moistened with water. At least six films per formulation should be studied, and then the mean and standard deviation determined. Films may also be placed on agar gel at a concentration of 1.5 percent w/v, after which pH paper is applied; the resulting color shift indicates the film's surface pH [82].

Interactional Angle

The wetting behavior, disintegration time, and dissolution of oral film may be predicted using contact angle measurements. These measurements are taken using a goniometer and are best taken at room temperature. The contact angle should be measured using double-distilled water. A single drop of double-distilled water is placed on the surface of the dried film. Within 10 seconds of falling, water droplets may be photographed with a digital camera. The image 1.28v program (NIH, USA) can examine digital images for angle determination [83].

Transparency

The films' transparency may be measured using a simple UV spectrophotometer. Film samples were trimmed into rectangles and placed on the spectrophotometer's glass slide. The films' transmittance should then be measured at 600 nm. The following criteria were used to establish the films' transparency:

The formula for determining how see-through something is is: b = c = (logT600).

In this equation, T600 represents the amount of light that can pass through at 600 nm; b= represents the thickness of the film in millimeters; and c= represents the concentration.

1

Moisture content

The drug content of each film is determined using the appropriate quantification technique, and then the films are filtered after being dissolved in a suitable solvent to ensure content consistency. In this context, a relative standard deviation of 6% or less is considered acceptable.

The created film was weighed, then dried using cadmium chloride desiccators to measure its moisture content. The percentage of moisture loss in the film was calculated by reweighing it after three days [84].

% Moisture content = Initial weight − Final weight X100 / Initial weight

Disintegration test

The amount of time (in seconds) it takes for a film to completely dissolve when exposed to liquids like water or saliva. This research may make use of pharmacopeial disintegration testing equipment. The average film decomposes in 5-30 s.

a. The Use of a Slide Show

One drop of distilled water was placed on the oral films using a pipette. The films were then affixed to the surfaces of slide frames and petri dishes. 1 The length of time it took for the film to degrade to the point where a hole could be seen through it was recorded.

b. Techniques using Petri dishes

One film was put on top of 2 ml of distilled water in a petri dish, and the time it took for the film to fully dissolve was recorded.

Dissolution tests in vitro

Dissolution is the rate at which drug material enters the solution per unit time under controlled circumstances of liquid/solid interface, temperature, and solvent concentration. Any of the basket or paddle apparatuses listed in the pharmacopoeia may be used to conduct dissolution tests. The maximum dosage of API and the sink conditions will determine the dissolving medium. Dissolving medium should be maintained at 37± 0.5°C with a rotating speed of 50. The oral films have the issue of floating above the dissolving medium while utilizing the paddle equipment [80].

The Organoleptic Test

Products having a sweet flavor are often well-received. Products are evaluated using carefully curated human taste panels. Taste sensors, custom equipment, and adapted pharmacopeial release mechanisms are utilised in in vitro approaches for this purpose [84].

Stability

When performing a stability study, it is important to adhere to the recommendations set out by the International Conference on Harmonization (ICH). The finished medication came in a special package. Butter paper was used for the first layer of protection, followed by aluminum foil, and finally a heat-sealed aluminum bag. Formulations should be kept in either a 30°C/60% RH or 40°C/75% RH storage environment. After three months, the films were analyzed for their drug content, disintegration time, and overall look [85].

A Quantitative Analysis of Adhesiveness

Tack is measured in the same way as pressure-sensitive adhesives are: by touching them and seeing how they feel.

Calculating the Percentage Yield

The % yield of buccal patches may be calculated using the following formula:

Obtained yield percentage = Mass of Buccal Patches x 100 Sum of medication and polymer mass

Values of pH at the Surface

The surface pH may be measured by putting the film in a petri dish that has previously been wet (with 0.5 ml-1 ml distilled water) for 30-60 seconds. The pH meter is utilized by touching the electrode to the film's surface, at which point a stable equilibrium is reached. When dissolved in 4 cc of distilled water, the pH may be measured using a calibrated pH meter [90].

Assessment of Clinical Risks

Oral irritation from the Quick-Dis TM formulation has been tested in both animals and humans. The formulation was given to the hamster twice daily for up to 4.5 days (nine doses total) in a research that included the use of the animal's cheek pouch. Clinical safety investigation of Quick- Dis TM was conducted using healthy human individuals to assess for irritation of the mouth mucosa [91].

Packaging

Protecting an oro-dispersible thin film requires expensive packing using a special procedure and careful thought. A variety of packaging options are available for this purpose, with aluminum pouches being the most widespread. Oral films must be individually packaged. APR -Labtec has invented a packaging technique for rapidly dissolving thin films called "Rapid card," which is about the size of a credit card and has a propensity to contain three strips on each side [92]. Typically, packaging material will need to: • Be approved by the Food and Drug Administration (FDA); • Be safe and unreactive; • Keep the formulation safe from the elements.

Tamper-proof test.

Wrapped with plastic, aluminum foil, or folded paper

As a result of its flexibility, the pouch is considered to provide not just tamper-resistant packing but also a high level of environmental protection [93].

Aluminum pouches that are both single-use and reusable

This thin film bag dissolves quickly, can be peeled open, and provides excellent protection and visibility. It is possible to utilize a laminated low-cost foil on one side of a transparent laminated structure. There must be no permeation of air or moisture through the lamination. It is possible to utilize the same packaging for both pharmaceuticals and nutraceuticals. The product and its composition are preserved inside the sealed bag. It's the standard for most packaging needs.

Multiple-item blister card

The blister card is made up of two pieces: the product compartment and the cover stock. Whether a rigid or semi-flexible blister is chosen depending on how much defense is required. Blister cavities are often made of plastic, whereas the stock for the top is made of aluminum foil.

Protective layers

Due of their susceptibility to moisture, many formulas need strong protective layers. Moisture may be kept out with the use of a number of different materials, such as Polychlorotrifluoroethylene (PCTFE) film, Polypropylene, etc. In terms of keeping air and moisture out, polypropylene is unrivaled. It can bend without breaking and will not stress fracture under any conditions. The lack of definition is a concern [94].

Recent studies have shown the deleterious effects of polymerization on film.

Influence of Polymers on Oral Films

Elevated Potassium Losartan Thin films for use in the mouth

Losartan potassium fast-dissolving oral thin films were created by N. G. Raghavendra Rao and colleagues using HPMC polymer with viscosity of 15 cps and 50 cps, at a concentration of 1000 mg and 750 mg, respectively. The aforesaid polymer concentrations resulted in a disintegration time of 50–90 seconds. Losartan potassium had a near-complete release pattern within 30 minutes

of in-vitro dissolution when polymers were present at the aforementioned quantities [95].

Caffeine thin coating that dissolves quickly in the mouthFarhana Sultana et al., developed fast dissolving oral thin films of caffeine in which HPMC (15cps), sodium alginate and kollicoat were used in concentration of 1500-2500 mg, 750mg, 750-1250 mg respectively. In these films with above concentration of HPMC the disintegration time obtained was in range 15-45 sec, for sodium alginate the disintegration time obtained was in range 20-35 sec and for kollicoat the disintegration time obtained was in range 15-30 sec. Further using in-vitro dissolution study, the release pattern of caffeine was about 100% within 100-300 sec, 150-250 sec and 100-200 sec for HPMC, sodium alginate and kollicoat respectively. Thus exhibiting faster release of caffeine with lowest concentration of kollicoat polymer [96].

Fast dissolving drug delivery system of Salbutamol sulphate

N.L. Prasanthi et al. employed a combination of hydroxy propyl cellulose (HPC), hydroxy propyl methylcellulose (HPMC), and sodium alginate (in concentrations of 0.5 to 2 mg, respectively) to create fast-dissolving oral thin films containing Salbutamol sulphate. The disintegration times of these films ranged from 1.5 to 2.5 minutes, 2 to 80 minutes, and 25 to 60 minutes, respectively, indicating that the disintegration duration is more variable when HPMC is employed as a polymer than when HPC or sodium alginate are [97].

Oral thin films of Sumatriptan succinate

To speed up the absorption of the migraine medication Sumatriptan succinate, Buchi N. Nalluri et al. created fast-dissolving oral thin films of HPMC E5, HPMC E15, and Polyvinylpyrrolidone (PVP) at concentrations of 650 mg, 650 mg, and 2 mg, respectively. Preparations for the samples were made using HPMC with and without PVP. Using the petri dish method, we determined that the disintegration time for HPMC E5 was 25-30 seconds, for HPMC E15 it was 31-37 seconds, and for HPMC E5 with PVP it was 9-10 seconds, demonstrating that a reduction in disintegration time was observed when using a combination of HPMC and PVP polymers. In addition, when HPMC E5 was utilized in conjunction with PVP, 100% of the Sumatriptan succinate was released in only 10 seconds. Although 100% release was achieved in 40-60 seconds when using HPMC E5, and in 100-120 seconds when using HPMC E15 [98].

Fast dissolving films of Levocitirizine dihydrochloride

Levocitirizine dihydrochloride thin films were created by Prabhakara Prabhu et al. with the objective of creating a dosage form with a very rapid beginning of action, which is useful in the treatment of severe allergic reactions. Polymers like HPMC and PVA, alone or in combination, were used to make levocetirizine dihydrochloride films. The disintegration time ranged from 10-34 seconds for films made with solely HPMC as the polymer to 58-106 seconds for films made with only PVA. The disintegration period was measured to be 32-130 seconds when using either polymer alone, but it increased to a much longer duration when using both. In conclusion, HPMC polymers with low viscosity allowed for faster disintegration [99].

Mouth dissolving film of Etoricoxib

When K. Senthilkumar and C. Vijaya wanted to create a thin film of Etoricoxib, they turned to HPMC E15 polymer with a concentration of 150 mg. The aforesaid polymer concentrations resulted in films with a disintegration time of 8-10 seconds and a release rate of about 100% after 30 minutes of in-vitro investigation. This further shown that HPMC polymer's low viscosity helps achieve quicker dissolving and rapid disintegration [100].

Oral disintegration thin films of Lovastatin

P. Pragathi et al. created a lovastatin thin film containing 4.5 mg of gelatin and 3.5 mg of PVA polymer. The obtained disintegration times for these films with the aforementioned concentrations of gelatin and PVA fell in the intervals of 10–72 seconds and 7–70 seconds, respectively. This demonstrated that the quicker breakdown was attained at lower PVA concentrations[101].

Rupatadine fumarate oral fast-dissolving films

Rapidly disintegrating Rupatadine fumarate oral thin films were created by A. Roy et al., who employed Pullulan, HPMC E 5, and E15 in doses of 300–400 mg, 400–500 mg, and 400–500 mg, respectively. The obtained disintegration times for these films with the aforementioned concentrations of Pullulan, HPMC E5, and E15 were 30-32 seconds, 28-37 seconds, and 36-38 seconds. In addition, an in-vitro dissolution study showed that the release pattern of Rupatadine fumarate at the aforementioned doses was around 100% within 180 seconds[102].

Microemulsion Loaded Sublingual Film of Fentanyl Citrate

D. Mundhey et al. used HPMC E5, and HPMC E15 at concentrations of 50mg and 20-50 mg, respectively, while creating thin films of Fentanyl Citrate. A mixture of 50 milligrams of HPMC E5 and 22.6 milligrams of HPMC E15 had a disintegration time of 20 seconds. In addition, an in-vitro dissolution investigation revealed that the release pattern of fentanyl citrate was almost 100% after 5 minutes when used at the same dosages. Oral dissolving films have recently been a hot subject of discussion among academics. Table 1 summarizes the limited number of research on formulation that have been done in the last several years [103][104].

Future Prospects

Technology for administering drugs orally has come a long way in the pharmaceutical sector. Traditional pills and capsules have been replaced with fast-acting, dissolvable films. Many factors, including the poor absorption of oral solid medications, the difficulty in giving injections, and the inaccuracy of dosing with liquid formulations, have prompted pharmaceutical firms to concentrate on developing innovative oral dosage forms. To overcome these obstacles, rapid dissolving oral thin films have been developed. Several oral thin films may be purchased without a prescription, therefore the idea is not novel. Prescription medications have been adapted into oral thin films due to their widespread popularity and the rising demand for similar goods sold over the counter. Both large pharmaceutical corporations and smaller biotech startups are showing interest in this new field. Many firms are working on various kinds of oral thin films using technology they've developed in this area (e.g. oral dispersible, sublingual, buccal). Oral thin films are being developed for a number of hormones and vaccines with the same goal in mind as the pharmaceuticals: to increase patient adherence to treatment. MonoSol Rx, Applied Pharma Research/Labtec GmbH, BioDelivery Sciences, and NAL Pharma are some of the major participants in this industry. Oral thin films are being used by several corporations in conjunction with these technology providers as a means of managing the lifespan of their branded pharmaceuticals after they lose patent protection for other dosage forms. Oral thin films aren't widely prescribed at the moment, but there's a lot of potential in the pipeline. Despite concerns about development, approval, and penetration, the industry is expected to expand steadily over the next decade. If the product is clinically and regulatoryly identical to an already approved oral drug product in the United States, the US Food and Drug Administration (FDA) will approve it via the Abbreviated New Drug Application (ANDA) process. Unlike the original drug, there is no need for clinical trials as part of the generic approval procedure (section 505 (j) of the Food, Drug, and Cosmetic Act). An ODT formulation and an ODF product, for instance, may be compared for bioequivalence to illustrate this point. However, the pharmacokinetic profile of the newly created oral film product may vary from that of the already marketed product. As a "new dosage form," the ODF must go through the rigorous approval procedures outlined in Section 505 (b) (2). In such a scenario, fresh clinical research is needed. An benefit of doing a new clinical research is that it might provide the product three years of commercial exclusivity. If the chemical is the same as the one already on the market, there is no need for further preclinical toxicity testing. Such studies are meant to show that a treatment is safe, well tolerated, and effective. Animal models and

human subjects both undergo testing for oral mucosa irritation. With the fast development of new technologies for preparing thin films, the industry's future is bright.

Table1: Recent Research Trends of Films Formulation.

S. No.	Name of research topic	Year
1	Formulation and Evaluation of Fast Dissolving Film of Imipramine Hcl	2022
2	The Optimization and Evaluation of Flibanserin Fast-Dissolving Oral Films	2022
3	Preparation and characterization of oral fast dissolving of Hydralazine HCL	2022
4	Formulation, Optimization and Evaluation of Nanoparticulate Oral Fast Dissolving Film Dosage Form of Nitrendipine	2021
5	Development, In Vitro and In Vivo Evaluation of Racecadotril Orodispersible Films for Pediatric Use	2021
6	Improved bioavailability of montelukast through a novel oral mucoadhesive film in humans and mice	2021
7	Optimization and evaluation of venlafaxine hydrochloride fast dissolving oral films	2020
8	In vitro and in vivo characterization of domperidone-loaded fast dissolving buccal films	2020
9	Preparation and Evaluation of Fast Dissolving Oral Film of Losartan Potassium"	2020
10	Prolonged release from orodispersible films by incorporation of diclofenac-loaded micropellets	2019
11	Fast Dissolving Oral Film of Piroxicam: Solubility Enhancement by forming an Inclusion Complex with β-cyclodextrin, Formulation and Evaluation"	2019
12	Formulation and Characterization of Fast-Dissolving Sublingual Film of Iloperidone Using Box– Behnken Design for Enhancement of Oral Bioavailability"	2018
13	Formulation and evaluation of fast dissolving film of lornoxicam	2018

Conclusion

Benefits of tablets (precise dose, convenient administration) and liquid dosage forms (long half-life) are combined in films (easy swallowing, Rapid bioavailability). Therefore, several pharmaceutical firms are switching production to oral thin films with a shorter time to effect. Oral thin films meet a demand in the market by allowing people of all ages, including children and the elderly, to take their medication without drawing attention to themselves and at any time of day or night. This technology lays the groundwork for creating items without patents and for prolonging the life of existing patents. Rapid dissolving oral thin films have a variety of uses beyond buccal fast dissolving systems, such as gastro-retentive and sublingual administration systems. Among the potential uses for fused multilayer films is the incorporation of otherwise incompatible active medicinal components into a single composition. An inert film layer may be sandwiched in between the two potentially dangerous pharmacologically active components. Inserting a thin film into the buccal or sublingual area causes the film's active pharmacological components, which have high transmucosal flow rates, to disintegrate slowly. Controlled-release polymer coatings for drugs are also an option. A lot of people are looking at this technology because they know it has a lot of untapped potential. Given the above, it is reasonable to draw the conclusion that oral fast dissolving films are an alternative to traditional dosage forms, offering the benefits of improved bioavailability, quick onset of action, and patient compliance at a lower manufacturing cost. These dosage forms are useful for loading a wide variety of powerful medicines and extending the patent life of older pharmaceutical items. Several studies have been published recently that may aid in the industrialisation of this innovative dosage form.

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