

A REVIEW ON FAST-DISSOLVING ORAL FILM**KOMAL A KAWALE, NEHA B AUTADE, HARSHDA S NARHARE, RAKSHA L MHETREA****Department of Pharmaceutics, PES Modern College of Pharmacy (for Ladies), (Affiliated to Savitribai Phule Pune University),
Pune, Maharashtra, India.*****Corresponding author: komalkawale2000@gmail.com***Received: 16 April 2023, Revised and Accepted: 29 May 2023***ABSTRACT**

Due to their increased comfort and flexibility, fast-dissolving oral films are the most cutting-edge oral solid dose form. It increases the effectiveness of APIs by dissolving in the oral cavity in under a minute after coming into touch with less saliva than fast-dispersing tablets, without chewing, and without the requirement for water for administration. Some patients, especially those who are young or elderly, have trouble chewing or swallowing solid dose forms. The fear of choking prevents many young and geriatric patients from taking these solid preparations. Consequently, orally dissolving pills have been developed. Due to consumer demand for a fast-dissolving product over conventional tablets or capsules, OTFs have gained a position as an alternative in the market. Depending on the film thickness and choice of the polymer matrix, these films can be adjusted to release the medicine more gradually. These films typically disintegrate in seconds to release the active ingredients. When a dosage form is placed on the tongue or in the oral cavity, it can swiftly hydrate, adhere, and dissolve, allowing for rapid local or systemic drug delivery. This type of dosage form is referred to as a film or strip.

Keyword: Fast dissolving film, Conventional tablet and capsule, Polymer matrix, Thin film delivery system.

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INTRODUCTION

Considering oral administration accounts for over 52% of the market for drug delivery overall, there has been a lot of interest in the development of modified-release oral dosage forms. The pharmaceutical industry's sources of drug leads have seen a tremendous shift in recent years [1]. However, there are some issues that are frequently connected to the oral administration of medications that reduce the danger of partial active component loss through tablet or capsule crushing or inaccurate liquid administration, which causes dose errors and overdosing or ineffective drug therapy. The screening regions of absorption, distribution, metabolism, and excretion follow the idea of large chemical space and narrow target space [2]. Fast-dissolving medication delivery systems are getting a lot of attention as a solution to these problems. In recent years, oral film strips have become popular as a brand-new method of breath freshening. These wafers, which resemble gel, disintegrate swiftly in the mouth to release flavor. Many pharmaceutical corporations have been diverted by recent technical breakthroughs to investigate new possibilities in this technology to give quick, accurate dosing that is anticipated to grow compliance, especially among young people. Transmucosal methods of drug administration have developed significantly in recent years because they have the potential to solve issues related to oral medication administration. The dose of medicine is swallowed after melting without the use of water or measurement. Because the mouth mucosa is highly vascularized and hence extremely permeable, absorbing drugs through it into the systemic circulation is a desirable strategy. As a result, fast-dissolving films have gained popularity as an oral dosage form for many medications since they offer quick disintegration due to their huge surface area [3]. Pharmaceutical technologists created a number of mouth-dissolving drug delivery devices to meet these medicinal needs. These films typically dissolve in water at ambient temperature, disintegrate in 30 s, and vanish in a minute. The drug's absorption and beginning of therapeutic impact occur more quickly the faster it dissolves in the solution [4]. Fast-dissolving films are often formed of plasticized hydrocolloids or mixtures of them that can be laminated through hot-melt extrusion or solvent casting. Depending on the properties of the film-forming substance, there may be a number of serious problems with the production of the dosage forms. Foaming during film production

brought on by material heating or solvent evaporation, flaking during slitting, and cracking during cutting are common issues. The films ought to be durable against moisture over time [5]. These benefits increase patient compliance and encourage pharmaceutical companies to spend money managing the current medicines on the market for MDFs [6]. Given its fast plasma half-life and high first-pass metabolism, it is a prime option for quick-release drug delivery systems [7]. Therefore, a combination of buccal/sublingual distribution with oral films seems like an appealing drug delivery method for patients [8]. When it comes to ease of handling the formulations, attractive appearance, and ease of usage, the mouth-dissolving film formulation beats out the liquid dosage form. Due to its pleasant taste and improved tongue feel, oral medicated mouth dissolving film displays increased patient compliance [9]. Due to chemical entities' poor aqueous solubility and lipophilic character, scientists are currently confronting their biggest difficulty. Due to their lipophilic nature, these medications can be targeted through the mouth, which improves their absorption. Due to its abundant blood supply, the mucosal cavity is greatly preferred [10]. Fast-dissolving intraoral films (FDF) are non-bulky oral dose forms with a number of benefits over traditional oral dosage forms [11]. Oral films, one of the many paths investigated, are receiving greater interest as a brand-new platform for patients [12]. These films are regarded as a preferred dose form because of their high durability [13].

To create new dosage forms, numerous pharmacological studies have been carried out, with the majority of these efforts concentrating on drug simplicity while taking the quality of life into consideration [14]. The oral bioavailability of medicines can be improved by enhancing their solubility or dissolving rate [15]. All of the aforementioned criteria for a viable solid oral dosage form for local drug delivery are met by quickly disintegrating films [16].

On the other hand, the oral cavity is very well tolerated by patients, the mucosa is relatively permeable with a strong blood supply, it is resilient and recovers quickly from stress or damage and the absence of virtually all Langerhans cells makes the oral mucosa tolerant to potential allergens. In addition, oral transmucosal drug administration prevents presystemic elimination in the GI tract and first-pass impact. These elements render the oral mucosal cavity an extremely desirable and practical location for

systemic medication administration. The drug is subsequently released for mucosal absorption or, with formula adjustments, will keep the quick-dissolving characteristics to enable gastrointestinal absorption when ingested [17]. For compounds with low skin penetration, buccal administration provides a great platform for absorption. Intercellular material formed from the so-called membrane coating granules found at the top 200 m layer of the oral mucosa serves as the main barrier to permeability in this tissue. Depending on the active medicinal ingredient, these dosage forms have a shelf life of 2–3 years; however, they are particularly susceptible to moisture in the environment [18].

Drug delivery within the oral mucosal cavity can be divided into the following three types:

- sublingual delivery, which involves systemic drug administration through the mucosal membranes lining the floor of the mouth;
- Buccal delivery, which involves drug administration through the mucosal membranes lining the cheeks; and
- Local delivery, which involves administering drugs directly within the oral cavity [19].

THIN FILM DELIVERY SYSTEM

Drugs are delivered to the systemic circulation using thin films that disintegrate in a technique known as “thin film drug delivery.” referred to as dissolving films or strips that, when placed in the mouth without any liquid or chewing, disintegrate in 1 min.

A user would normally place a dissolving film or strip on, under, or along the inside of the cheek while administering medication orally. The thin film offers an alternative for individuals with swallowing issues and patients experiencing nausea, such as chemotherapy patients, because it dissolves quickly without the need for water. The first fast-dissolving dosage form to be created was a tablet, and the quick-dissolving qualities were gained through adjustment to the formulation or unique process [20]. Powerful medicines with short plasma half-lives have their effects for a longer period while maintaining a constant plasma level of the drug [21].

Fast-dissolving films are becoming more popular recently as an alternative to fast-dissolving pills for treating patients with obstructions and removing their fear of choking. Plasticized hydrocolloids typically make up fast-dissolving films. Foaming during film production brought on by material heating or solvent evaporation, flaking during slitting, and cracking during cutting are all problematic. The films need to be flexible, exhibit appropriate tensile stress, be stable to moisture, make handling easier, and not adhere to packaging materials or fingers [3]. Hold unique advantages over other solid dosage forms due to their thickness and compact size, which encourages patient compliance [22]. An ideal mucoadhesive system adheres to the site of attachment for a few hours, releases the drug in a controlled manner, aids in the rate and extent of drug absorption, does not irritate the patient or cause them any discomfort, does not interfere with their ability to talk, drink, or perform other daily activities, and offers unidirectional drug release toward the mucosa [23]. Excellent accessibility makes it simple to apply, localize, and remove the medication [24]. The majority of commercially available formulations, such as Listerine PocketPaks™,3, Ora-film™,1 (benzocaine), and Theraflu®,2 (dextromethorphan/phenylephrine HCl, diphenhydramine HCl/phenylephrine HCl, or diphenhydramine HCl), are made to deliver locally acting medications [25]. New administration strategies for current medications are frequently much less expensive to develop, leading to increased efficacy and bioavailability as well as reduced dose frequency to lessen adverse effects [26].

To achieve effective medication therapy, it is necessary to overcome a number of advantages and drawbacks, including the following [27]:

Advantages

Advantages include:

- Simple transportation.
- Ease of swallowing for elderly and young patients.

- No water is required for administration, which makes it convenient for dysphasic patients who have trouble swallowing pills and capsules.
- Stability and rapid commencement of action with enhanced bioavailability thanks to avoiding the hepatic first-pass effect [28].

Disadvantages

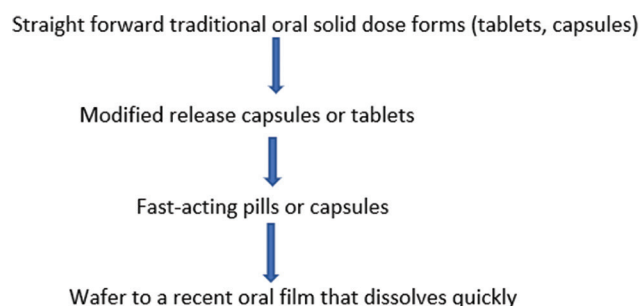
- Drugs that become unstable at buccal pH cannot be given.
- Drugs that irritate the mucosa cannot be given by this route of administration.
- A medication with a low dose requirement can only be given.
- Taste masking is necessary because the majority of medications have a bitter taste [29].

DEVELOPMENT OF ORAL SOLID DOSE FORM

At the moment, there is a lot of interest in developing the oral delivery of medications with poor water solubility [30]. The most fruitful field of medication delivery innovation research has been oral therapy [31].

The formulation for oral solid dosage has through a number of stages of development [32].

To address the most important and urgent issue in drug development, the idea of giving medications after lag is being further investigated [33].



COMPOSITION OF THE MOUTH-DISSOLVING FILM

Different additives can affect this process and the structure of a film [34].

API

It is possible to provide a range of active pharmacological substances.

High-dose medications are challenging to include in the movie due to a restriction on the size of the dosage form. Ideal dynamic voice for oral films pharmaceutical ingredients (APIs) should ideally be strong, highly lipophilic, and less bitter. About 5% w/w to 30% w/w of the dry film is made up of the drug, and up to 10% w/w of the dry film can be made up of multivitamins. Both children and many adults dislike active pharmacological substances that have a bitter taste and/or irritate the mouth and throat [35].

Ideal characteristics

- The dosage of the drug to be included should be as low as 40 mg.
- Smaller and more moderately sized molecules of drugs are preferable.
- The medication needs to be stable and soluble in saliva and water.
- At the pH of the oral cavity, the medication should be partially unionized.
- The oral mucosa must allow the medication to pass through [36].

Film-forming polymer [37]

The water-soluble polymers give the films quick disintegration, a pleasant mouthfeel, and mechanical qualities. Brand-new polymers utilized in medicine delivery [38]. By increasing the molecular weight of the polymer film bases, the disintegration rate of the polymers is slowed down. HPMC E-3 and K-3, Methylcellulose A-3, A-6 and A-15, Pullulan (The creation of pullulan was a logical extension of Hayashibara's

original 1883-founded enterprise, which was the manufacture of starch syrup. Hayashibara began marketing Pullulan films in 1982.) [39], Carboxymethyl Cellulose Cekol 30, Polyvinylpyrrolidone PVP K-90, Pectin, Gelatin, Sodium alginate, Hydroxypropyl cellulose, Polyvinyl alcohol, Maltodextrins, and Eudragit-RD10 are some of the water-soluble polymers used as film formers. POLYMERIC FILMS are being used in a wider variety of pharmaceutical research, development, and dosage form creation processes. There is currently no coating technique that can compete with film coating in terms of production capacity or cost-effectiveness for coating tablets and other solid dosage forms [40].

A brand-new polymer that forms films is polymerized rosin.

Plasticizer

It has been noted that formulation concerns (plasticizer, etc.) are significant factors determining the mechanical characteristics of films. To choose an appropriate plasticizer and solvent, preliminary research was done [41]. Plasticizers have also improved the mechanical characteristics of the films, such as their tensile strength and elongation. These qualities might be impacted by variations in their concentration. Glycerol, di-butylphthalide, and polyethylene glycols are the most widely used plasticizers [42].

Surfactant

Surfactants are employed as solubilizing, wetting, or dispersing agent to dissolve the film quickly and release the active ingredient [43]. The Ostwald-Freundlich equation, which links the drug's small particle size and, if relevant, its amorphous state, to an increased solubility.

The important element in determining the pace and degree of absorption is solubility [44]. Benzalkonium chloride, benzethonium chloride, tweens, and sodium lauryl sulfate are a few of the often-utilized substances. As a solubilizing, wetting, and dispersion agent, poloxamer 407 is one of the most significant surfactants.

Sweetening agent

Sweeteners now play a crucial role in medicinal medicines that are meant to dissolve or disintegrate in the mouth. It is well known that food preferences are heavily influenced by the sweetness of flavor [45]. In these situations, the bitter taste is frequently a major issue [46]. Sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose are the traditional sources of sweetness. Since many oral-delivery medications have unpleasant properties including bitterness, sourness, saltiness, or inducing oral numbness, taste-masking technologies are crucial for achieving high patient compliance and drug therapy efficiency [47]. The temporal profiles of sweetness show how the perception of sweetness changes over time [48].

The use of artificial sweeteners in pharmaceutical formulations has grown. The first generation of artificial sweeteners consists of saccharin, cyclamate, and aspartame, while the second generation includes acesulfame-K, sucralose, alitame, and neotame. Making use of flavors and sweets in the formulation is necessary for physical taste masking [49].

Saliva stimulating agent

Faster dissolution of the fast-dissolving film formulations is facilitated by increased saliva production. Acids that are used to prepare food should therefore be present in the formulations as salivary stimulants. A few examples of salivary stimulants include citric acid, malic acid, lactic acid, ascorbic acid, and tartaric acid, with citric acid being the most popular.

Flavoring agent

You can choose flavoring agents from artificial flavor oils, oleo resins, and extracts made from different plant components like leaves, fruits, and flowers. An unpleasant taste is one of the numerous significant formulation issues that are present with some medications [50]. You can use flavors individually or in combination. Any flavor can be added,

including water-soluble menthol extracts, fruit essences such as apple, raspberry, cherry, and pineapple, as well as potent mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, and clove. Sour fruit flavors like lemon and orange can also be added. The type and strength of the flavor determine how much flavor is required to cover up the taste.

Coloring agent

Titanium dioxide is one of the FD and C approved coloring compounds that are used in the production of orally rapid dissolving films, with concentration levels not exceeding 1 percent (w/w) [51].

METHODS OF PREPARATIONS FOR THE FILM

There are several methods employed for the manufacturing of such dosage forms such as casting, spraying, and extrusion [52].

Method of preparation of fast-dissolving films fast-dissolving films can be prepared by:

- Solvent casting method
- Semisolid casting method
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method.

Solvent casting method

This process involves dissolving the medicine along with various excipients in a suitable solvent while also dissolving water-soluble polymers in the solvent. The two solutions are then combined and agitated. The air bubbles in this solution are subsequently settled by degassing it under a vacuum. The final step is to cast the bubble-free solution into a Petri dish and let it dry. The base of the current film preparation is easily dissolved in saliva without forming insoluble materials, and it has been used in oral care products to treat foul breath [53].

Advantages

- Better clarity and thickness uniformity compared to extrusion.
- The film has a nice shine and is devoid of flaws like die lines.
- Film has better physical qualities and is more flexible.
- Although different thicknesses are achievable to suit API loading and dissolving requirements, the recommended finished film thickness is typically 12–100 μ m.

Disadvantages

- The polymer needs to be water or a volatile solvent-soluble.
- It should be possible to generate a stable solution with a suitable minimum solid content and viscosity.
- It must be feasible to create a homogeneous film and be released from the casting support.

Semisolid casting method

This procedure creates a water-soluble film-forming polymer solution. Then the resultant solution is mixed with an acid-insoluble polymer solution (e.g., cellulose acetate phthalate and cellulose acetate butyrate). The right quantity of plasticizer is then added to create a gel mass. The films or ribbons are then cast using heat-controlled drums from the gel bulk. The films should be between 0.015 and 0.05 inches thick. The ratio of the film-forming polymer to the acid-insoluble polymer should be 1:4.

Hot melt extrusion

This procedure makes use of a hot melt extruder. In this method, a polymer is heated and then shaped into a film. A mixture of dry pharmaceutical materials, including API, is added to the hopper; transported, mixed, and heated before being extruded out in molten form by the extruder. The film is cast using the molten mass that has now solidified. The casting and drying process is a crucial phase. This method has a lot of benefits, such as the possibility of continuous operation, minimal product waste, good control of operating

parameters, shorter residence times and lower temperatures for the drug carrier mix, absence of organic solvents, and scalability.

Advantages

- No solvent or water is required
- The API's compressibility characteristics might not be significant
- A superior substitute for drugs that are not easily soluble
- Greater uniformity of dispersion due to vigorous mixing and agitation
- Requires less energy than high-shear methods.

Disadvantages

- Thermal deterioration brought on by the use of high temperatures.
- The polymer's flow characteristics are crucial for processing.
- The scarcity of available polymers.
- No excipient may contain any water or other volatile solvents [54].

Modern drug delivery methods

By creating a solid dispersion or solid solution, melt extrusion has been employed in the pharmaceutical industry for a variety of goals, including:

- Enhancing the drug's bioavailability and dissolving rate.
- Regulating or altering the drug's release.
- Covering up a drug's unpleasant aftertaste.

Solubility and permeability are the two key factors that affect a drug's bioavailability when taken orally. The introduction of high throughput screening in the drug development process has led to the creation of molecules that are frequently quite large in size, highly lipophilic, and poorly soluble. Scientists have experimented with numerous medicinal interventions to try and solve the solubility problems. The creation of solid dispersions and solid solutions is one of the numerous current technologies available to increase solubility and the rate of dissolution.

Solid dispersion extrusion

When one or more active chemicals are dispersed in an inert carrier in a solid form while amorphous hydrophilic polymers are present, this is referred to as solid dispersion. In this process, medications are dissolved in suitable solvents before being added to the polyethylene glycol melt at a temperature below 70°C. Finally, using dies, solid dispersions are molded into the films [55].

Pharmaceutical applications with solid dispersions

Since 2003, more than 80 oral thin film brands have been introduced in North America; however, the market is still small compared to ODTs. However, the OTF sector is well-positioned in terms of future growth [56].

Up to 50% of the new drug candidates discovered as a result of high-throughput screening has very low solubility and thus low bioavailability. It can be difficult to produce pharmaceutical products when solubility, dissolution rate, and absorption of medications with low water solubility are problematic. Solid dispersions are a strategy to improve the API's solubility and bioavailability, which is partly accounted for by a decrease in particle size.

Based on the drug's solubility in the carrier, solid dispersions can be categorized as molecular or particulate. The words molecular dispersion or solid solution is used when the medicine is disseminated at the molecular level.

Rolling method

In the rolling procedure, a drug-containing solution or suspension is rolled 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. Using a high-shear processor, additional materials, including the active substance, are dissolved in a tiny amount of aqueous solvent. Hydrocolloids that are water soluble are dissolved in water to create a homogeneous viscous solution [57].

EVALUATIONS OF THE FILM

Pre-formulation research is required to reach the set objective [32].

Thickness

It is important to ensure uniformity in the thickness of the film since the thickness of a film directly affects the uniformity of the drug content. In many key areas, it can be measured with a micrometer screw gauge or calibrated digital Vernier Calipers. The film should have a thickness between 5 and 200 micrometers.

Dryness test

It has been determined that there are roughly eight stages in the drying process of a film: 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. The majority of the studies can be meticulously modified to analyze pharmaceutical OFDF even though the tests are generally

Table 1: Formulation table

S. No	Components	Concentration
1.	API	1–25%
2.	Film-forming polymer	45%
3.	Surfactant	q. s
4.	Plasticizer	0–20%
5.	Sweetening agent	3–6%
6.	Flavoring agent	Q. S
7.	Coloring agent	Q. S
8.	Vehicles	Q. S
9.	Saliva stimulating agent	Q. S

Table 2: List of pharmacological molecules that can be included in the oral strip is shown in the table

Active pharmaceutical ingredients	Therapeutic action
Loperamide	Anti-diarrheal
Famotidine	Antacid, anti-diarrheal
Azatadine maleate	Anti-histaminic
Tripolidine hydrochloride	Anti-histaminic
Chlorpheniramine maleate	Anti-allergic
Ketofren	Analgesic

Table 3: List of certain polymers that produce films

Synthetic polymer	Natural polymer
Methylcellulose	Starch
Hydroxypropyl cellulose	Pectin
Hydroxyethyl cellulose	Gelatin
Hydroxypropyl methyl cellulose	Xanthan
Polyvinyl alcohol	Pullulan
Kollicoat IR	Maltodextrin
Sodium carboxy methyl cellulose	Sodium Alginate

Table 4: Available film in the market [80]

S. No	Drug	Dose per day	Therapeutic action
1	Famotidine	10 mg/day	Antacid
2	Loperamide	2 mg/day	Anti-diarrheal
3	Azetidine maleate	1 mg/day	Anti-histaminic
4	Tripolidine hydrochloride	2.5 mg/day	Anti-histaminic
5	Chlorpheniramine maleate	4 mg/day	Anti-allergic
6	Nicotine	2 mg/day	Smoking cessation
7	Ketoprofen	12.5 mg/day	Analgesic
8	Loratadine	10 mg/day	Anti-histaminic
9	Sumatriptan succinate	35–70 mg/day	Anti-migraine
10	Aciravastine	8 mg/day	Anti-histaminic

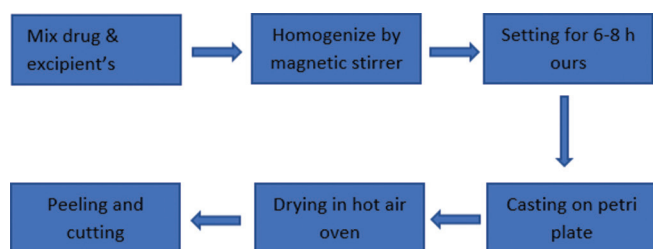


Fig. 1: Solvent casting method

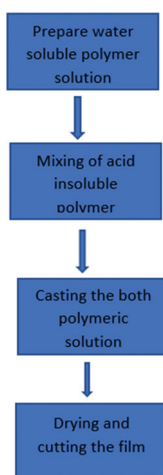


Fig. 2: Semi solid casting

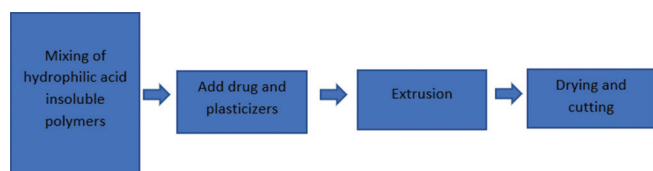


Fig. 3: Hot melt extrusion

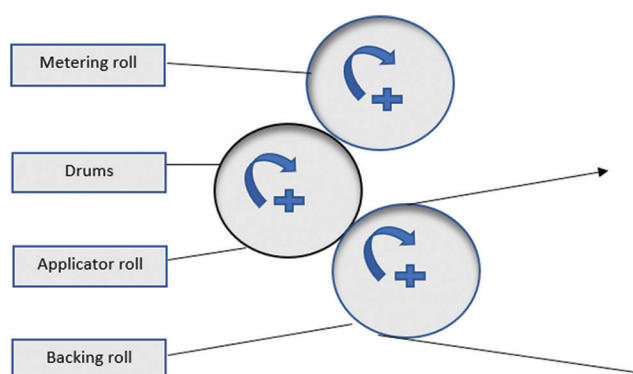


Fig. 4: Rolling method

designed to evaluate 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 paper) after being rubbed on it. For this investigation, there are also instruments available [58].

Wt. variation

From each film formulation, three 2 cm² films were randomly selected. Films were individually weighed using an automated scale, and Each batch's mean weight was computed.

Surface pH

Surface pH 2.5.4 0.5 ml of phosphate buffer was then used to wet it, and it was left for 30 s. After putting the electrode of the pH meter in touch with the formulation's surface and giving it a minute to equilibrate, the pH was recorded. For each formulation, Average data were provided after the studies were carried out in triplicate [59].

Folding endurance

It was discovered by repeatedly folding a film with a constant cross-sectional area and thickness until it snapped. The folding endurance value is calculated as the number of folds a film might endure without breaking. This test validates the film's tensile strength.

Uniformity of drug content

Consistency in medication content.

The drug content of all batches was calculated using random sampling.

The phosphate buffer was used to dissolve the FDF (22 cm²). This mixture was filtered before being added to the HPLC. A mean of three measurements was used to determine the drug content [60].

Percentage elongation

The following formula is used to compute percentage elongation by measuring the growth in length of the film following the measurement of tensile strength.

$$\text{Elongation as a Percentage} = [L-L_0] \times 100 / L_0$$

L₀ was the starting length, while L was the final length.

Film coatings can boost overall film strength, minimizing dust generation and lowering the coefficient of friction in metal chutes thanks to their lower elasticity modulus and stronger tensile fracture strength [53].

Stability study

It describes how important physical stability is for pharmaceutical products as well as how to assess it for tablets, capsules, suspensions, emulsions, solutions, and ointments [61].

The chosen formulas were packaged in aluminum foil to completely and flawlessly cover the film. After that, they were kept at 40°C and 75% relative humidity for a month 4–8 weeks in a humid environment [62], and at certain intervals, their physical characteristics and *in vitro* drug release were assessed [43]. or

Three-monthly stability studies were conducted in the humidity chamber at 35°C and 65% relative humidity for all batches. The films were assessed for their drug content, rate of disintegration, and physical look after three months [63].

In vitro Disintegration time

Three films from each formulation were taken and tested for disintegration by being placed in a Petri dish with a wall height of 1.3 cm and a surface area of 6.3 cm² that contained a buffer solution with a pH of 6.8. It is noted when the picture started to fall apart. We computed the mean and standard deviation.

In vitro dissolution studies

Using a pH 6.8 phosphate buffer solution, a 3-min *in vitro* dissolution experiment was conducted on films of selected formulations. Dissolution media was maintained at 37 0.5°C and 50 rpm. Every 30 s, the samples (5 mL) are removed and replaced with new pH 6.8 phosphate buffer solution. After that, 10 mL of the 5 mL samples were diluted in a volumetric flask. Using a U.V. spectrophotometer set to a maximum wavelength of 256 nm (Electro Lab Ltd Dissolution Apparatus used for dissolution investigations), the samples' drug concentration was ascertained. Increased dissolution rate can be attributed to a strongly enhanced surface area of the drug for dissolution [64].

FTIR

Studying compatibility using FT-IR spectroscopy, IR grade KBr was separately mixed with pure drug and drug coupled with polymers, then transformed into KBr pellets by a hydraulic press and scanned across a range of 4000–400 cm^{-1} [19].

XRD

To ascertain the crystallinity of raw medications and drugs included in films, X-ray diffraction was used. For the purpose of analyzing the amorphous/crystalline behavior of treated medicines, diffraction patterns were acquired [18].

Studies on differential scanning calorimetry (DSC)

To ascertain potential interactions between the medication and excipients, DSC experiments were carried out using a Perkin-Elmer DSC-4 system, calibrated using an indium standard [65].

Film-forming capacity

Film-forming capability is a polymer's capacity to create the desired strip.

It is divided into categories based on its ability to form strips, such as very poor, poor, average, good, better, and best.

Appearance of films

Using visual cues such as transparency and semitransparency, the strip's appearance was assessed [66].

Drug release kinetics

The release data were fitted to the following kinetic models to study the mechanism of drug release.

Kinetics of zero order $Q_t = Q_0 + k_0t$

Where Q_0 is the starting dose of the medication in the pharmaceutical dosage form, Q_t is the dose at time t , and k_0 is a zero-order rate constant.

Initial-order kinetics $\ln Q_t = \ln Q_0 + k_1t$ or $Q_t = Q_0 e^{-k_1t}$

Where Q_0 is the initial concentration of the drug in the solution, Q_t is the amount of drug released at time t , and k_1 is the first-order release constant. Dissolution efficiency (DE) was proposed by Khan as a useful metric for the assessment of *in vitro* dissolution data [67].

In vitro microbiological studies

In vitro, microbiological experiments were conducted to verify that the antibacterial activity was still present after being liberated from the films. For this, the antibacterial activity of the aliquot removed from each film of the formula after 35 min of the *in vitro* drug release experiment (the time at which films indicate complete dissolving) was assessed. A common bacterium that causes dental plaque and cavities, *Streptococcus mutans*, is tested for antimicrobial activity. The antimicrobial studies' protocol followed the findings of Jagtap and Karkare's investigation [68].

Testing for mechanical strength

A texture analyzer TX was used to examine the films' mechanical strength [69].

Porosity

The liquid displacement method was used to calculate the porosity of the ChS film and nanocomposite films [30]. An electronic balance machine (W1) was used to measure the weight of each dried film. The dried film was then placed in an ethanol-containing beaker for 24 h, and the weight was recorded as W2. Finally, the film was taken out of the ethanol, and W3 was recorded as the weight of the beaker holding the leftover ethanol. The following formula was used to compute porosity: % porosity = $(W_2 - W_1 - W_3 / W_2 - W_3) \times 100$ [70].

Tensile strength

A load cell-equipped Fudoh Rheometer (JJ, Rheotech, Japan) was used to measure the mechanical characteristics. Two grips that are 1.5 cm

apart were used to fix the films, and they are then pulled continuously. The peak stress, or the level at which the films burst, was noted. Three different film samples made using the same formulation were used for three different measurements.

Fracture force/cross-section area equals tensile strength [71].

APPLICATION OF MOUTH-DISSOLVING FILM**Vaccines**

Fast-dissolving buccal films can administer vaccines that are stable at room temperature and easily dissolve in saliva and the mouth. Rotavirus vaccine made in the United States is a fast-dissolving buccal film that is stable at room temperature and makes vaccinations virtually as simple as mouthwash. Improved patient compliance, increased bioavailability, and a decrease in the expenses of handling, administration, and storage are just a few of the benefits that this delivery system offers.

Controlled and sustained release film

Chitin and chitosan derivatives, among other polymers, are utilized as excipients in hospital preparations for the sustained-release buccal film.

Taste masking

Fast-dissolving tablets must include taste masking to be successful commercially. Fast-dissolving buccal films dissolve or break down in the patient's mouth, releasing the active substances that come into touch with the taste buds. This quality is therefore crucial for the patient's compliance. By using solvent evaporation and solvent extraction procedures, medications with an unfavorable bitter taste can be microencapsulated into acrylic polymers that are pH sensitive. These polymer microspheres demonstrated quick and complete disintegration as well as effective taste masking.

Orally disintegrating film

Fast-dissolving buccal films are based on a water-soluble polymer that dissolves when ingested. Patients with swallowing issues and patients experiencing nausea, such as those getting chemotherapy, have an alternative thanks to the film's capacity to dissolve quickly without the need for water [72].

PACKAGING OF MOUTH-DISSOLVING FILM

Storage, protection, and stability of the dosage form depend heavily on packing concerns. Barrier films, single pouches, aluminum pouches, blister packaging with multiple units, and foil paper or plastic pouches are among the packaging options for oral thin films.

For medications that are particularly moisture-sensitive, barrier films are most frequently used. There is ample room for logos, codes, directions, or other information on primary packaging constructed of a sealing pouch thanks to Labtech GmbH's rapid film technology. The films are created by a laminating process, and the cost of packaging is similar to that of tablets [73].

MDFs in biopharmaceutical consideration

Before creating a new dosage form, it is important to take biopharmaceutical considerations into account. Fast-dissolving oral films dissolve instantly, making it easier for the medicine to be absorbed through the oral mucosa from the mouth, throat, and esophagus. Age, the makeup of the mouth cavity, and blood flow there should all be taken into account. Drug distribution is influenced by factors such as tissue permeability, perfusion rate, medication binding to tissue, and drug interactions. The amount of time it takes for the drug to leave your body or reach its target depends on how quickly it leaves. Different characteristics, such as the patient's age, sex, and health, have an impact on the dose form's pharmacodynamic performance [74]. Throughout the trial, adverse occurrences were gathered [75]. Such a decline in food quality might be prevented by edible films and coatings [76].

The panel of human taste

The study was carried out in accordance with the ethical principles derived from the Declaration of Helsinki and followed the ICH-GCP guidelines of January 17, 1997, and was in compliance with local regulatory requirements. It was approved by the Ethical Committee of the University deli Study di Milano. All participants were fully apprised of the necessary information and the study's objectives. Each subject received a written consent form, read it, understood it, and signed it before tasting test samples.

Ten healthy subjects each tasted a 0.50 mL aliquot at random. All samples were held in the mouth for 15 s before being removed, the individuals gargled thoroughly, and at least an hour passed before tasting the next one [77]. Bitterness were measured by the consensus of a trained taste panel, with 20 mg of each sample held in the mouth for 5–10 s, then spat out; the bitterness level was then recorded [78].

Tests for taste masking

Using an Electronic tongue (E-tongue), formulation complexes were examined *in vitro* for their effectiveness at disguising taste. The electronic tongue is a device that evaluates and contrasts the flavors of various solutions. The three levels of biological taste recognition are mirrored by the electronic tongue: the receptor level (probe membranes in the E-tongue mimic human taste buds), the circuit level (transducer mimics neural transmission in humans), and the perceptual level (computer and statistical analysis mimic human thalamic cognition). This method shortens timescales and enables researchers to simultaneously collect taste and dissolution data. An array of seven sensors and a 16-position autosampler make up the Electronic Tongue system (Alpha M.O.S., France) employed in this investigation [79].

PRODUCTION OF ODFS [80]

All ODFs were created using the solvent casting technique and a Coat Master® 500 automatic film applicator (Erichsen, Hemer, Germany) working at a speed of 6 mm/s. Before the examination, ODFs were tightly stored in sealed aluminum sachets after being dried for 12 h at room temperature. An ODF measuring 20 mm by 30 mm has a 15 mg medication dose.

ODFs for immediately released drugs

Drug (2.1%), glycerol (6%), HPMC (15%), and distilled water (76.1%) were used to create ODFs with immediate drug release (ODFIR). They were produced using a 1200 mm gap width.

Two-layer ODFs drug-containment

Using a gap width of 800 m, the drug layer is created using drug (3.13%), glycerol (6%), HPMC (15%), and distilled water (75.87%).

After drying, EC (16%), glycerol (4%), and ethanol absolute (80%) are combined to create the second layer, which is the water-insoluble shielding layer. Directly on top of the drug layer, the shielding layer is cast with a gap width of 400 micrometers.

ODFs with prolonged drug release

To create ODFs with prolonged drug release (ODFPR), hot-melt extruded matrix particles (MPs) that are drug-loaded were added to the polymer solution that forms ODFs. Drug made up 30% of MPs, together with silicon dioxide (0.5%) and Eudragit® RS (69.5%). The ODFs were created at a gap width of 1200 m after preparing the ODF-forming polymer solution, which included HPMC (15%), anhydrous glycerol (6%), and distilled water (72.06%). MPs having a size of <315 m that exhibit somewhat extended drug release were found in ODFPR 315. For the creation of ODF, MPs with a size range of 500–715 m that exhibit highly delayed drug release were employed.

TECHNOLOGY

Quick-DISTM

To meet the market's unmet needs, Lavipharm Laboratories Inc. (Lavipharm) has created the perfect intraoral fast-dissolving

medication delivery system. The new intraoral medication delivery method, trademarked (TM) Quick-Dis, is a thin, flexible, and quickly dissolving film and is a patented, proprietary technology of Lavipharm. The tongue's top or bottom is where the film is placed. It quickly releases the active ingredient for local and/or systemic absorption while being maintained at the application location. Unit-dose pouches to multiple-dose blister packages are just a few of the packaging options available for the Quick-Dis medication delivery system.

The Quick-Dis™ film, which has a thickness of 2 mm, often disintegrates in about 5–10 s after coming into contact with water. This is known as the disintegration time. The dissolving time for Quick Dis™ film with a thickness of 2 mm is approximately 30 s, where the dissolving time is defined as the time at which not <80% of the tested film is dissolved in aqueous conditions. A Quick-Dis™ medication delivery method typically exhibits a 50% release of an active component within 30 s and a 95% release within 1 min.

Soluleaves

A variety of oral delivery films that can include active substances, colors, and flavors are created using technology. When in contact with saliva, SOLULEAVE™ films can be made to swiftly dissolve, releasing the flavors and active substances.

Wafertab

This is a medicine delivery device that includes pharmaceutical ingredients in a filmstrip that may be swallowed. When the strip comes into contact with mouth saliva, the system quickly dissolves and releases the active ingredients. To further enhance taste masking, the WAFERTAB™ filmstrip can be flavored. Because the active component is properly dosed and integrated into the structure of a pre-fabricated XGEL™ film, needless heat and moisture are avoided, potentially improving product stability.

Foam burst

This unique SOLULEAVE™ technology variation involves passing an inert gas through the film as it is being created. As a result, a film is created with a honeycomb structure that quickly dissolves and produces a novel tongue experience. Manufacturers of foods and confections are interested in FOAMBURST™ as a flavor delivery system.

XGEL

All of Meldex International's film systems and its innovations for ingestible dosage distribution involve film, which is at the core of the company's intellectual property. With its nonanimal origin, religious approval, and suitability for vegetarians, XGEL™ film offers special product benefits for healthcare and pharmaceutical products. It is also GMO-free and continuous production processing offers a cost-effective and competitive manufacturing platform. The XGEL™ film has the capacity to include active pharmacological compounds and can also be taste-masked, colored, layered, and have enteric qualities [11].

LITERATURE SURVEY

Future possibilities

Technologies for oral drug delivery have advanced significantly in the pharmaceutical sector. The market has advanced significantly from traditional tablets and capsules to contemporary fast-acting tablets and films. Pharmaceutical companies have shifted their focus to creating novel oral dosage forms that overcome a number of problems, including poorer bioavailability of oral solid medications, the inconvenience of delivering injections, and erroneous dosing by liquid formulations. The majority of these difficulties are addressed by fast-dissolving oral thin films. The idea is not brand-new, and there are numerous oral thin films that can be purchased without a prescription. Prescription medications have been transformed into oral thin films thanks to positive user feedback and rising demand for over-the-counter oral film solutions. Pharmaceutical companies, old and new, are both paying attention to this developing field [91].

S. No	Drug	Disease	Dosage form	Aim	Conclusion	References
1.	Ondansetron	Nausea and vomiting	Oral mucoadhesive film	Ondansetron hydrochloride mucoadhesive films were designed for the prevention and treatment of chemotherapy-induced emesis.	Films offer a sustained release, which can support delayed emesis.	[81]
2.	Paracetamol	Fever and pain	Mouth dissolving film	Fast dissolving drug delivery systems, like MDF, are cutting-edge dosage forms that dissolve or disintegrate inside the mouth.	Within 30 min, the improved formulation demonstrated a 92% drug release. The manufactured strips appear to be a desirable replacement for traditional commercial formulations.	[82]
3.	Aspirin and acetaminophen	Arthritis pain, fever.	Oral dissolving film	To develop and evaluate physicochemical properties of acetaminophen and aspirin orally disintegrating strips with high loading dose.	Even one month following the stability assessment, ODFs of APAP and aspirin prepared using the solvent casting process demonstrated acceptable mechanical characteristics and adequate% drug release.	[83]
4.	Atenolol	Hypertension	Oral disintegrating film	The study's major goals were to develop the oral disintegrating films loaded with atenolol using the solvent-casting method and to conduct evaluation tests on them.	Furthermore, prepared oral disintegrating films can be considered a different way to provide atenolol.	[84]
5.	Cetirizine and dextromethorphan	Allergic asthma and throat infection	Fast dissolving film	The study's goal was to develop and improve a fast-dissolving film for dextromethorphan and cetirizine flavor masking utilizing a casting method using HPMC E5 LV, polyethylene glycol 400, aspartame, neotame, tartaric acid, citric acid, and menthol ion exchange resins.	Conclusion: Without using any organic solvents, a fast-dissolving film containing cetirizine and dextromethorphan may be cast using the solvent casting process.	[85]
6.	Cilnidipine	Hypertension	Fast dissolving film	The goal is to formulate cilnidipine into solid dispersions and incorporate those into the formulation of fast-acting films that dissolve quickly to increase its solubility and oral bioavailability.	In the current work, the solid dispersion approach using a carrier such PEG 400 was used to increase the solubility of cilnidipine, and the optimized formulation was added to the fast-dissolving film.	[86]
7.	Propranolol HCL	Hypertension, migraine prophylaxis	Sublingual film	The current investigation's goals were to create and assess an oral fast-dissolving sublingual film containing propranolol HCL.	As a result, the manufactured fast-dissolving film of propranolol HCL may be a superior option to tablets and capsules in the treatment of migraine prophylaxis by obtaining quick oral bioavailability.	[87]
8.	Olmesartan medoxomil	Hypertension	Buccal patch	Olmesartan Medoxomil Fast Dissolving Buccal Patch Formulation and Evaluation.	The fast-dissolving buccal patch of Olmesartan medoxomil was successfully formulated to achieve a safe, rapid and effective dosage form with enhanced drug dissolution and rapid antihypertensive therapy.	[6]
9.	Telmisartan	Hypertension	Fast dissolving film	To produce a telmisartan-containing fast-dissolving film for the treatment of hypertension.	Using the solvent casting method, fast-dissolving films were created using hydroxypropyl methylcellulose, polyvinyl alcohol, glycerol, sorbitol, menthol, and an alkalizer. Weight, thickness, folding endurance, appearance, tensile strength, disintegration time, and dissolution profile of optimized formulations were assessed.	[88]

10.	Tramadol hydrochloride	Pain	Orally disintegrating film	The goal of the current study is to create and assess orally disintegrating films of tramadol hydrochloride that dissolve within 30 s.	Without the use of any wetting or solubilizing agents, pullulan film disintegrated more quickly.	[89]
11.	Etoricoxib	Pain, inflammation, fever	Mouth dissolving film	The goal is to develop a mouth-dissolving film of etoricoxib for the treatment of pain.	To sum up, by creating an inclusion complex with beta-cyclodextrin in a 1: 1 g ratio, etoricoxib MDF was created with improved solubility and tolerable taste masking.	[90]
12.	Dicyclomine	Stomach pain, muscle spasm.	Fast dissolving oral film	The purpose of this study is to develop and assess the enhanced bioavailability of pharmaceuticals in comparison to traditional solid oral dosage forms (FDOF) of the anticholinergic medication dicyclomine.	This work demonstrates that fast-dissolving films of dicyclomine HCL can be created with the goal of improving patient compliance and therapeutic efficacy by boosting bioavailability.	[91]
13.	Desloratadine	Hay fever, allergy	Oral strip	The aim to Optimization and Evaluation of Desloratadine Oral Strip: An Innovation in Pediatric Medication.	The work that was just described was an attempt to create a unique OS of DSL for pediatrics use that would get beyond the issues with liquid dosage forms that are often given to kids during AR.	[41]
14.	Loratadine	Hay fever, conjunctivitis.	Fast dissolving film	The goal is to create and assess loratadine fast-dissolving films using the solvent casting method.	Good mechanical properties were demonstrated for the produced formulations.	[42]
15.	Zolmitriptan	Migraine, headaches.	Fast dissolving oral film	Fast-dissolving oral films of zolmitriptan formulation and evaluation.	For quick absorption, the produced films were found to be consistent, flexible, and 98.5% of the medication was released from the F5 film in <6 min.	[43]

CONCLUSION

Both mucoadhesive and Oro dispersible films have been successfully used as effective drug delivery platforms, particularly for proteins and peptides, thanks to the prominent characteristics of oral films, including fast drug absorption, high bioavailability, easy-to-use nature, and avoidance of the first pass effect both in GI tract and in the liver. The development of fabrication techniques, as well as formulation strategies using both natural and synthetic polymers, has advanced oral films significantly for their practical uses. In addition, actives could be enclosed in nanoparticles or inclusion complexes, which are uniformly or unevenly distributed into the oral films produced, not only to nicely enhance the bio adhesion to the targeted oral mucosa but also to sufficiently improve both the solubility and permeability of the corresponding drugs, ultimately resulting in a fully promoted drug absorption and highly enhanced bioavailability. Despite the aforementioned advancements, there are still several obstacles that prevent such alluring oral films from being widely industrialized and commercialized. Future research must, on the one hand, concentrate on the creation of innovative formulations that increase drug loading rates while simultaneously taking biocompatibility and biodegradability into account. On the other hand, it is necessary to adapt the production techniques now in use to enable the creation of these newly developed oral films with a reduced processing time and increased output.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The author declares no conflict of interests

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