Exploring The Versatility Of Oral Dispersible Films : A Comprehensive Review

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Abstract- **In the late 1970s, rapid disintegrating drug delivery system was developed as an alternative to capsules, tablets and syrups for geriatric and pediatric patients having problems in swallowing. To overcome the need, number of orally disintegrating tablets which disinter grate within one minute in mouth without chewing or drinking water were commercialized. Then later, oral drug delivery technology had been improved from conventional dosage form to modified release dosage form and developed recently rapid disintegrating films rather than oral disintegrating tablets. Oral disintegrating film or strips containing water dissolving polymer retain the dosage form to be quickly hydrated by saliva, adhere to mucosa, and disintegrate within a few seconds, dissolve and releases medication for oro mucosal absorption when placed in mouth. Oral film technology is the alternative route with first pass metabolism. This review give a comprehensive detail of materials used in ODF, manufacturing process, evaluation tests and marketed products.**

Key points: **Oral disintegrating film, oral strip, pediatric and geriatric patients.**

1. 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 presystolic 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: i. ii. 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 iii. Local delivery, which involves administering drugs directly within the oral cavity [19].

2. 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 PocketPaksTM,3, Ora-filmTM,1 (benzocaine), (dextromethorphan/phenylephrine and HCl, Theraflu®,2 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]

2.1 Advantages of Orally Dissolving Films (28)

1.Convenient dosing.
2. No water needed.
3. No risk of chocking.
4. Taste masking.
5. Enhanced stability.
6. Improved patient compliance.
7. The drug enters the systemic circulation with reduced hepatic first pass effect.

8. Site specific and local action.
9. Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
10. Dose accuracy in comparison to syrup.

2.2 Disadvantages of orally dissolving films

1.The disadvantage of orally dissolving film is that high dose cannot be incorporated into the strip.
2. The dose should be between 1-30 mg.
3. There remain a number of technical limitations with use of film strips; the thickness while casting the film.
4. Glass Petri plates cannot be used for casting.
5. The other technical challenge with these dosage forms is achieving dose uniformity.
6. Packaging of films requires special equipment's and it is difficult to pack.

2.3 APPLICATIONS OF ORAL FILMS IN DRUG DELIVERY

Oral drug delivery by sublingual, mucosal and buccal become preferable for therapies in which immediate absorption is required including those used to manage pain, allergies, sleep problems and CNS disorders. Topical applications, the oral films are ideal in the delivery of active agents like analgesic or antimicrobial ingredients for the care of wound and other applications. Gastroprotective dosage systems, poorly soluble and water-soluble molecules of different molecular weights are found in film format (Barnhart and Sloboda, 2007a). Dissolution of oral films could be initiated by the pH or enzymatic secretion of GIT and are used to treat gastrointestinal disorders. Diagnostic devices, Oral films loaded with sensitive reagent to allow controlled release faced to biological fluid for separating multiple reagents to allow a timed reaction within diagnostic device [29].

3. CLASSIFICATION OF FAST DISSOLVING TECHNOLOGIES [30]

Orally dissolve technologies can be divided in to three broad groups.[31]

- Lyophilized systems.
- Compressed tablet-based systems.
- OTF

Properties	Lyophilized system	Compressed tablet-based system	Oral thin films
Composition	Solution or suspension of drug with excipients	Active pharmaceutical ingredient with super disintegrants	Hydrophilic polymers with drug and other excipients
Technology used	Lyophilization	Direct compression	Solvent casting, hot melt extrusion
Characteristics	High porosity which allows rapid water or saliva penetration & disintegration	Different levels of hardness and friability these result in varying disintegration and packaging needs	Large surface area leads to rapid disintegration
Packaging	Blister pack	High density polyethylene bottles	Blister cards with multiunit

3.1 Classification of orally dissolving films

1. Flash releasing oral films.
2. Mucoadhesive Melt-away wafers.
3. Mucoadhesive sustained-release wafers.

4. IDEAL PROPERTIES OF THE FILM FORMING POLYMERS. [32]

1. The polymer employed should be non-toxic, non-irritant and devoid of any leachable impurities.
2. It should be tasteless.
3. It should have good wetting and spread ability property.
4. The polymer should exhibit sufficient peel, shear and tensile strengths.
5. The polymer should be cheap and readily available.
6. It should have long shelf life.
7. It should not cause any secondary infections in the oral mucosa/ dental region.
8. It should have a good mouth feel property.
9. It would be ideal to have a polymer that would have local enzyme inhibition action.

5. METHODS OF PREPARATIONS [33-36]:

1. Casting and drying
   A] Solvent casting
B] Semisolid casting
2. Freeze-dried wafer
3. Extrusion
A] Hot melt extrusion
B] Solid dispersion extrusion
C] Rolling method

5.1. 1] Casting and drying

A] Solvent casting method

• First, prepare the casting solution.
• Then deaeration of the solution is done.
• Transformation of the solution is done.
• Transformation of the accurate volume of solution into a mold. After this, the casting of the dried solution takes place.
• Cutting the final dosage form takes place to contain the desired amount of the drug.
• Packing oral fast-dissolving films are prepared by dissolving strip-forming agents and plasticizers in distilled water. After this, the solution is continuously stirred for up to four hours by a magnetic stirrer and kept for one hour to remove all entrapped air bubbles. In separate containers sweetening agents, saliva-stimulating agents, flavor and drugs are dissolved with constant stirring for 45 min. After stirring, both solutions are mixed with going another by a magnetic stirrer. Keep the solution stable for 1 hour to settle down the foam. The resulting formulation is cast on a suitable platform and is dried to form a film. The film is dried or dried under the oven after this film is carefully removed.

B] Semisolid Casting method:

In this method, at first, a solution of water-soluble film-forming polymer is prepared. Prepared solution of insoluble acid polymer for, e.g. - (cellulose acetate phthalate, cellulose acetate butyrate) designed by ammonium, sodium hydroxide. After this correct number of plasticizers is added to get a gel mass. After this, a gel mass is cast into films using heat-controlled drums. The thickness of the film is about 0.015-0.05 inches.

5.2. 2] Freeze-dried wafer

It is a technique called lyophilization, a dehydration technique based on the sublimation of water in a product. This transitions from a solid to a gaseous state or from ice to vapor without going to a liquid form.

5.3. 3] Extrusion

A] Hot melt Extrusion:

It is a process of continuously applying heat and pressure to melt a polymer and forcing it through an orifice. In this hot melt, the extrusion drug is mixed with the carrier/ vehicle in the solid form. Extruders have the facility of the heater; it is used to melt the reliable form carrier and drug, then this melt product is placed in dies and cut into a different shape. This process does not need or use any solvent system. The hot melt extrusion process involves lower temperature, absence of organic solvents, continuous operation possibility, minimum project wastage, reasonable control of operating parameters, and the possibility to scale up. Extrusion equipment is classified into three main categories ram, radical screen and roll and screw extruders. Screw extruders are essential in the pharmaceutical industry due to it helps to convert feed material to the finished form like rod tube and film. Rotating screws force feed materials are softened by frictional heat developed by the barrel wall. The feed reaches of the screw in a viscous state that can be forced through an orifice and molded into a desired shape.

B] Solid dispersion extrusion:

A solid dispersion is defined as a formulation of poorly soluble compounds as solid dispersions might lead to particle size reduction, improved wetting, reduced agglomeration changes in the physical state of the drug and possibly dispersion on a molecular level by the physical form of solid dispersion. Solid dispersion extrusion refers to the dispersion of one or more active ingredients in an inert carrier in a stable state in the presence of amorphous hydrophilic polymers. In this method, the drug is dissolved in a liquid solvent. The solution is incorporated into the melt of polyethylene glycol, and lastly, solid dispersion is shaped into films by the use of dies.

C] Rolling method:

A solution or suspension containing a drug is rolled on a carrier. The Solvent is mainly water or a mixture of water and alcohol, and the film is dried on the rollers and out into desired shapes and sizes.

6. EVALUATION PARAMETERS

The films are evaluated after they have been created using one of the above-mentioned manufacturing processes. To preserve inter- and intra-batch homogeneity amongst films, evaluation is a vital and necessary stage. Numerous criteria are investigated and classified into categories based on their physical and chemical characteristics.[**39]**

6.1. Physical Parameters

Physical parameters are essential since they are applied to the final dosage form, providing information about the consistency between batches and helping to maintain the final formulation's visual appeal. Technical rules from other industries, such as the plastic industry, can be used as templates because the USP only specifies a tensile strength test for surgical sutures and patches. Tensile testing in accordance with the DIN EN ISO 527-1 and 527-3 regulations or the ASTM International Test Method for Thin Plastic Sheeting (D 882-02)15 can be used.[**38]**

7. MECHANICAL PARAMETERS

7.1. Tensile strength [40]

The greatest stress that can be given to a film specimen before it breaks is known as the tensile strength, and it may be calculated using the applied load at rupture as the mean of three measurements and the cross-sectional area of the fractured film using the equation below.

Tensile strength of film in N/mm2 = breaking strength (Newton) /cross-sectional area of the sample (mm2).

7.2. Dryness / Tack test

Tack is the strength with which the film attaches to any piece of paper that is put into contact with the strip, whereas dryness is the quality to measure the solvent or water content present in the film. It has been determined that there are eight distinct stages in the drying process for films: set-to-touch, dust-free, tack-free, dry-to-touch, dry hard, dry-through, dry to-recoat, and dry print free. These characteristics can currently be measured using many different equipment. This can be accomplished at lab scale by pressing the thumb against the film.

7.3. Young's modulus

The stiffness of a film is measured by its elastic or Young's modulus. The techniques used to calculate tensile strength could also be applied in this situation. It is shown as the following when the applied stress to strain ratio in the elastic deformation zone is used:

Young's Modulus = Slope x 100/Film Thickness x Cross Head Speed

A tough and brittle film exhibits a high Young's modulus and tensile strength with little elongation.

7.4. Percentage elongation

A type of deformation is elongation. Anything under stress simply changes shape, and a texture analyzer used to measure this change. In other words, a sample deforms, lengthens, or elongates when it is subjected to tensile stress. The following formulae used to determine it by measuring the increase in length of the film following tensile measurement:

(L-L0) X 100 / (L-L0) = Percent Elongation

L0 was the initial length, and L was the finished length.

7.5. Tear resistance

Plastic film or sheeting's tear resistance is a complicated function of its ultimate rupture resistance. The force needed to start tearing is essentially measured using a very modest loading rate of 51 mm (2 in.) /min. The tear resistance value is expressed in Newton's (or pounds-force) and represents the maximum stress or force (which is typically obtained close to the outset of tearing) needed to tear the specimen**.**

7.6. Folding endurance Film's flexibility is a crucial physical quality required for easy application on the administration site. The strength of the film can be quantitatively measured in terms of folding endurance by simply folding the mouth dissolving film at a 180° angle of the surface at the same layer until it fractures or by folding it three hundred times without breaking. The folding endurance value is calculated as the folding number of the film can endure without breaking.

8.1 OTHER PHYSICAL PARAMETER

8.1.1 Appearance

Any produced film can be examined to determine whether it looks transparent or opaque. Surface qualities are often determined through visual inspection, however tools like microscopes can also be utilized.

8.1.2. Thickness

Micrometer screw gauges used to measure the produced film's thickness at various key spots. Film thickness should be measured five times, starting from the center and moving outward from all four corners, before calculating the mean thickness. It is crucial to confirm uniformity in the film thickness because it has a direct impact on the strip's dosage accuracy.

8.1.3. Weight variation

Each film should be weighed individually, then the average weights should be determined. The particular weight of the film is then reduced by the weight of the films as a whole. A significant weight fluctuation suggests that the procedure used was ineffective and suggests that the medication content was likely not uniform**.**

8.1.4. Contact angle

At 37°C, contact angle can be determined with a goniometry (AB Lorentz and wetter, Germany). You can accomplish this by taking a dry film and dabbing a drop of distilled water on its surface. Digital cameras can capture images of water droplets within 10 seconds of their deposition. On both sides of the ISSN: 2250-1177 Journal of Drug Delivery & Therapeutics. 2023; 13(7):172-176 descent, the contact angle can be measured, and an average is taken.

8.1.5. Transparency

Simple UV spectrophotometers used to determine the films' transparency. Place the film inside the spectrophotometer cell after cutting it into a rectangular shape. Find the film's transparency at 600 nm. The following formula used to calculate the film's transparency:

Transparency = (log T600)/b = —єC.

T600 stands for transmittance at 600 nm, b for film thickness (mm) and C for concentration.

8.1.6. Moisture content

The brittleness and friability of films are impacted by the moisture content. In short, the product's ingredients control how much moisture is present in a given film. Generally, moisture content testing equipment, the Karl Fisher titration method, or the weighing method used to determine how much moisture is contained in the film. Usually, a pre-weighed film of a certain size is heated to between 100 and 120 °C until it reaches a consistent weight, and the difference in weight indicates the amount or level of moisture contained in the film.

% Moisture content= [(Starting mass - Final mass) 100/Initial weight] used to compute moisture content.

The optimal moisture content for a film is 5% or less.[**41]**

8.2. Chemical Parameters

8.2.1. Surface pH test

Agar gel with a 1.5% weight / volume ratio and pH paper with a pH range of 1 to 11 used to measure the surface pH of a film. It is noted and reported that pH paper's color changes.

8.2.2. Disintegration time

The film's dissolution and disintegration properties can be determined from the disintegration time. A stainless-steel wire mesh is filled with 25 ml of pH 6.8 simulated salivary fluid, and the necessary size of film (2 x 2 cm2) is placed inside of it. In vitro disintegration time is the amount of time it takes for film to break and dissolve.

8.2.3. Test for in vitro dissolution

The paddle or basket apparatus mentioned in the pharmacopoeias used to conduct dissolution testing. The sink conditions and API dose will primarily be taken into consideration while choosing the dissolving medium. The tendency of the strip to float onto the dissolving media when the paddle equipment is used frequently makes the dissolution test challenging.

8.2.4. Thermal analysis

A differential scanning calorimeter used to record thermo grams of the samples, which gives information about the status of the drug molecules within the film. Any re crystallization, phase change, or molecular interaction of the drug molecule enclosed inside the film is immediately represented by a shift in the endothermic or exothermic peak or a widening of peak area. This can be determined by heating the sample in an aluminum pan at a predetermined heating rate (about 10°C/min) from ambient temperature to an increased temperature (about 500 °C).

8.2.5. Crystallinity

By performing X-ray crystallographic investigations with an X ray diffractometer, it is simple to detect if the drug molecule inside the film is crystalline or amorphous. Films can be inserted in the sample holder, and an X-ray source used to acquire XRD transmission diffractograms over a start-to-end diffraction angle, scan range, and scan speed.

8.2.6. Assay / Uniformity of content

Standard assay technique specified for the specific drug candidate in the standard pharmacopoeias are used to determine uniformity of content. The consistency of the material is evaluated through determining the API content in every separate film. The maximum content uniformity is between 85 and 115%.

8.3. In vivo test

Measurements of the contact angle and thermo-mechanical analyses of the film swelling tendency have both been used to simulate in vivo disintegration. With the assistance of a tasting panel and live volunteers, in vivo testing primarily entails tasting the films and measuring their in vivo disintegration time. The taste of the movies is also evaluated using an electronic tongue tester.

8.4. Additional tests

Analyses of the polymer solution's viscosity, the homogeneity of the content, and the detection of residual solvents are additional techniques for characterizing and monitoring the quality of orally dissolving film. By using scanning electron microscopy, X-ray diffraction, and near-infrared chemical imaging, Garsuch and Breitkreutz discovered caffeine recrystallization in Mouth dissolving films changing between the upper and lower surface. Raman and near-infrared spectroscopy are suitable technologies to identify and measure APIs in the films. Crystalline and glass transition temperature are studied using differential scanning calorimetry, thermo-mechanical analysis, and X-ray diffraction. Isothermal calorimetry was used by Gaisford to monitor the crystallization of drug from Oral film. By using dynamic vapor sorption or by weight, researchers examine hygroscopic and residual water content. Further research about standard guidelines should be done on microbiological studies and stability tests. [**39]**

9. CONCLUSION:

This review shows that mouth dissolving films are promising dosage form as they have more patient compliance and rapid onset of action. Moreover, they are potential candidate for oral route as they can deliver drug locally as well as systematically. MDF are used for pediatric and geriatric population or for patient those who have difficulty in swallowing. Due to these advantages MDF used to treat patient efficiently.

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