

ORALLY DISINTEGRATING FILM – A MODERN APPROACH IN DRUG DELIVERY SYSTEM

Abstract

Innovative methods of drug delivery have gained more attention in recent times in an effort to boost patient compliance, safety, and effectiveness. The search and creation of novel chemical molecule is a expensive and time-consuming. As a result, the pharmaceutical businesses are concentrating on creating novel drug delivery technologies for their current product lines. The quick disintegrating oral film is one such delivery method that has grown in popularity among geriatric and pediatric patients. When inserted in the mouth, orally disintegrating film or strips retaining the dosage form to be rapidly hydrated by saliva and with water dispersing polymer dissolve in a matter of seconds and release the medication into the oromucosal cavity. This chapter gives a detail of merits, demerits of orally disintegrating film, components, manufacturing process and critical quality attributes.

Keywords: patient compliance, orally disintegrating film, taste masking, solvent casting, saliva stimulating agent.

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I. INTRODUCTION^[1,2]

The oral route the most widely used routes of drug administration since it is safe, easy to administer, and acceptable to patients. Nearly 60% of conventional dosage forms are available as oral solid dosage forms. However, the parenterals and liquid dosage forms were chosen by the manufacturer owing to dysphagia, prolonged onset of action, and low absorption of oral solid dosage forms. However, the challenge of proper dosing with liquid dose forms (syrup, suspension, emulsion, etc.) and the discomfort associated with parenterals as a medication delivery route lead to non-compliance from patients.

Tablets and capsules are most popular oral dosage forms, but major drawback is the difficulty to swallow. People experience inconvenience in swallowing tablet dosage forms is inconvenient for geriatrics and pediatric patients having difficulty in swallowing and in case where water is unavailable like during traveling (motion sickness). Under such circumstances, dosage forms which can rapidly dissolve or disintegrate within the oral cavity have attracted an excellent deal of attention.

Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are the two examples of orally disintegrating dosage forms. Orally disintegrating films (ODFs), when placed on the tongue, will rapidly hydrates by soaking saliva which leads to disintegration and/or dissolution and releases active pharmaceutical ingredient from the dosage form.

II. THE ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA^[3]

The mucous membrane lining the interior of the mouth is called the oral mucosa. It is made up of a layer of stratified squamous epithelium known as "oral epithelium" and a layer of lamina propria, a connective tissue beneath it. Based on histology and function, the oral mucosa is classified into three primary categories:

1. The lining mucosa, which is a nonkeratinized stratified squamous epithelium, is present in the oral cavity practically everywhere else. Examples of this include,
 - a. The alveolar mucosa, which is the lining that lies between the buccal and labial mucosae. It has numerous blood vessels, is smooth, glossy, and bright red.
 - b. The buccal mucosa, which is a portion of the lining mucosa and lines the interior of the
 - c. Cheeks and mouth floor.
 - d. The labial mucosa, which is a portion of the mucosa lining the inside of the lips.
2. The keratinized stratified squamous epithelium known as the masticatory mucosa is located on the tongue's dorsum, the hard palate, and the gingiva that is connected.
3. Specialized mucosa, which is located in the areas where the tongue's dorsal surface hosts taste buds on lingual papillae, contains nerve endings for both taste perception and general sensory reception.

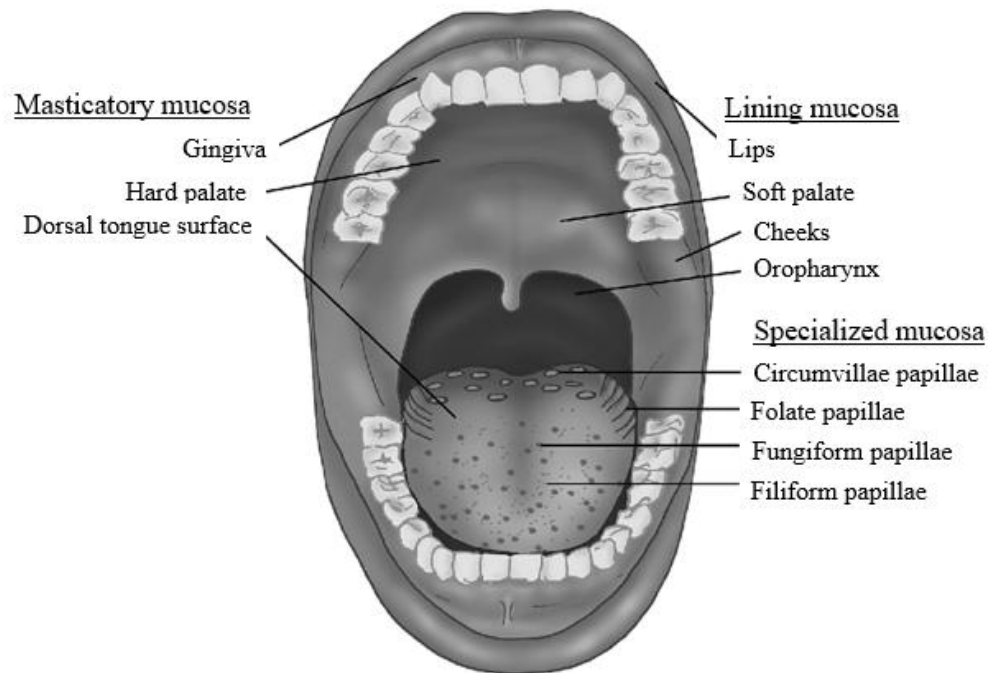


Figure: Oral Mucosa^[6]

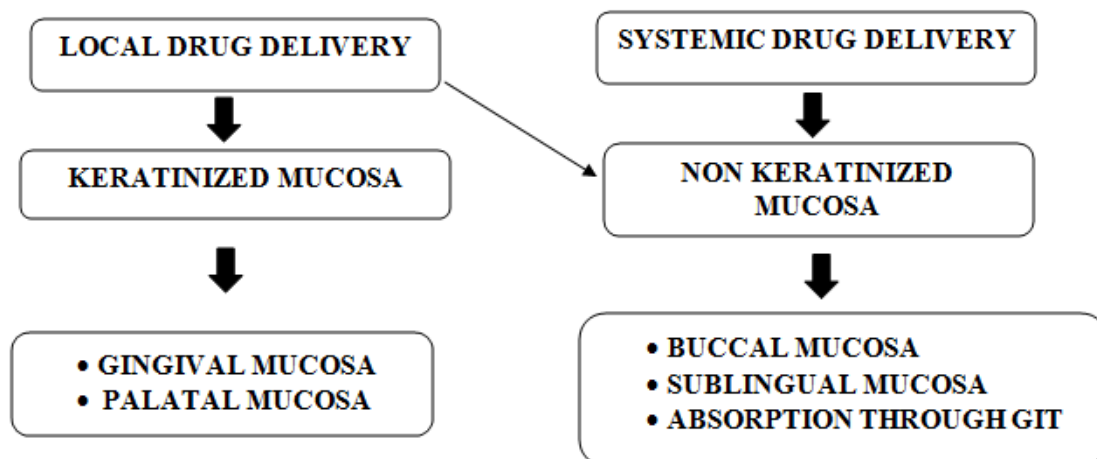
There are five tastes that are associated with distinct tongue receptors: sweet sensations are found at the tongue's tip, sour sensations are found at the sides, bitterness is found at the back of the tongue, and salty sensations are found at the sides and tip of the tongue. These taste receptors bind chemicals down by saliva and send electrical impulses to the parts of the brain involved in taste perception through the 7th, 9th, and 10th cranial nerves.

Food is softened by the enzymes and the salivary glands' moist environment, which makes swallowing easier and starts the digestive process. Saliva contains mucin, which is secreted by the salivary glands. The pH range of saliva is 6.8 to 7. It has been discovered that buccal mucosa has 4000 times more permeability than skin.

III. DRUG DELIVERY THROUGH ORAL MUCOSA^[4,5]

Drug delivery through the oral mucosa can be divided into 2 different approaches:

- a. Local Drug Delivery
- b. Systemic Drug Delivery



The Keratinized Mucosa, such as gingival and hard palatal mucosa, are yet not considered a valid site for the systemic administration of drugs, and they must be considered as useful sites for local (direct) drug delivery only in treating oral diseases occurring at the gingiva or palate.

Sublingual Drug Delivery: The systemic delivery of medication through the mucosa lining the floor of the mouth is known as sublingual drug delivery. This is typically utilized to deliver medications systemically to treat acute illnesses. Since the sublingual mucosa is thinner and more permeable than the buccal mucosa, it is a viable site to use if a quick onset is required.

Buccal Drug Delivery: Medication delivery through the buccal mucosa lining is known as buccal medication delivery. Because the buccal mucosa cannot give the quick commencement of absorption, it is far less permeable than the sublingual mucosa. Therefore, when the systemic treatment of chronic illnesses necessitates the sustained delivery of medications with systemic effects, the buccal mucosa represents the preferable route.

IV. ORAL FILM CLASSIFICATION ^[7,8]

Three types of oral films includes:

1. Flash release film
2. Mucoadhesive melt away wafer
3. Mucoadhesive sustained release wafer

Characteristics	Flash release film	Mucoadhesive melt away wafer	Mucoadhesive sustained release wafers
Structure	Single layer system	Single or multilayer system	Multilayer system
Nature of Excipients	Soluble, highly hydrophilic Polymers	Soluble, highly hydrophilic polymers	Low/ non-soluble polymers
Drug Phase	Solid solution	Solid solution or suspended drug particle	Suspension or solid solution
Site of application	On tongue (upper palate)	In the gingival or buccal region	Gingival (other region in the oral cavity)
Dissolution/ Disintegration time	60 seconds at most	Disintegrate in a few minutes and form a gel	Maximum 8-10 hours
Site of action	Both systemic or local	Both systemic or local	Both systemic or local

V. ADVANTAGES OF THIN FILM OVER CONVENTIONAL DOSAGE FORM^[9-13]

- Dissolution occurs rapidly as compared to conventional dosage form.
- The dosage form is easier to carry and less friable than the oral disintegrating tablet, which needs specific packaging.
- Advantageous over liquid dosage form that has poor stability and need of care to measure the appropriate amount and to shake the bottle every time before use owing to its less acceptability to patients.
- Ophthalmic dosage forms like solution and eye drops have a limitation of high ocular drug bioavailability and prolong duration of action.
- Ophthalmic film can be the alternative to better drug delivery to eye.

Clinical Advantages of Thin Film^[14-16]

- Patients favor thin film because of its appellative form and convenience of administration.
- It is appropriate for pediatric, geriatric, and psychiatric patients due to its ease of administration and lack of choking or suffocating risk.
- Ophthalmic films lengthen a medication's retention period, which increases the drug's absorption from the anterior part of the eye.
- Beneficial in case of bedridden and uncooperative patients.

- Helpful in situations when a quick start of action is needed, such as motion sickness, abrupt episodes of allergic reaction or coughing, bronchitis, or asthma.

VI. MAJOR LIMITATIONS OF THIN FILM^[15-19]

1. Low drug loading capacity limits the use of a less potent medicine at high dose.
2. Due to its hygroscopic nature special care is to be taken during storage.
3. Using a combination of drug is difficult task because it will hinder both disintegration time and dissolution rate.
4. The challenge of attaining a high degree of accuracy regarding the amount of medicine in each particular unit dose of the film might lead to therapeutic failure, non-reproducible effects, and occasionally hazardous effects for the patient.
5. Preparation requires excess time for drying.

VII. COMPONENTS OF FILM

The ingredients used in formulation of orally disintegrating film should be generally recommended as safe (GRAS) and approved by FDA and are as listed below:

- Active Pharmaceutical Ingredient (API)
- Polymer
- Plasticizer
- Sweetening agent
- Flavouring agent
- Coloring agent
- Saliva stimulating agent
- Taste masking agent

Detailed information regarding these components are as following:

Active Pharmaceutical Ingredient (API)^[1,8]

The amount of active pharmaceutical component that can be added to other excipients can range from 5 to 30% w/w. Depending on the required release profile, APIs can be loaded as nanoparticles or crystals, milled, or micronized. Before adding APIs to the movie, the flavor of bitter medications must be covered up.^[20] Many methods are employed to improve the flavor, but the most basic one is the obscuration approach, which consists of combining and co-processing an API that tastes bitter with an excipient that tastes pleasant.

Polymers^[8, 21-30]

In order to achieve desirable properties like disintegration time, drug loading capacity, mechanical strength, and drug release profile, the most crucial step in the development of ODFs is choosing the polymer or polymer mixtures to use as the drug-release matrices. The polymers should not induce infections in the oral mucosa, be inexpensive and commercially available, have a good shelf life, be non-toxic, non-irritating, and have high purity, adequate wetting and spreadability, sufficient feel, and good shear and tensile strength.

Natural Polymers	Synthetic Polymers
Pullulan	Carboxy methyl cellulose
Gelatin	Hydroxy propyl methyl cellulose
Pectin	Hydroxy Propyl Cellulose
Sodium alginate	Polyethylene oxide
Maltodextrin	Polyvinyl alcohol
Chitosan	Polyvinyl pyrrolidone

- Pullulan** - Made of neutral polysaccharide and maltotriose units, this water-soluble glucan gum has a low oxygen permeability. It is produced by *Aureobasidium pullulans*. Pullulan's superior film-forming qualities enable it to make films that are tasteless, transparent, flexible, soluble, odorless, heat-sealable.
- Gelatin:** Collagen is hydrolyzed or thermally degraded to make gelatin, which is mostly taken from the bones, hide, and connective tissues of porcine or bovine sources. Because of their low melting point, biodegradability, and edible nature, gelatin-based films offer special qualities and are clear, flexible. Gelatin films don't cost much.
- Chitosan:** Chitosan films provide advantageous toxicological qualities, excellent biocompatibility, low oxygen permeability, and biodegradability. Drug shelf life could be increased by the chitosan-based films' antibacterial and antifungal properties.
- Hydroxy Propyl Methyl Cellulose (HPMC):** consists of 3–12% hydroxypropyl (–OCH₂CHOHCH₃) groups and 19–30% methoxyl (–OCH₃) groups. The categorized degree of hydroxypropyl and methoxyl substitution as well as molar substitution is indicated by grade letters like E, K, J, and F. It is nearly insoluble in hot water, dehydrated alcohol, acetone, and toluene but soluble in cold water and forms a hydrocolloid. Frequently employed as a viscosity modifier, release controller, coating agent, excipient, and film former, it exhibits excellent film-forming properties along with outstanding biocompatibility and biodegradability.
- Hydroxy Propyl Cellulose (HPC):** a cellulose derivative whereby some of the hydroxyl groups have undergone hydroxypropylation, resulting in the formation of OHCH₂CHOHCH₃ groups. In cold water, HPC dissolves readily and forms a transparent, colloidal solution. It is soluble in many cold or hot polar organic solvents but insoluble in hot water. Because of its good film-forming ability and adequate mechanical qualities, including good carrying capacity, tolerable clarity, and moderate bioadhesion, HPC has been employed as a film former. One benefit of HPC is its broad spectrum of solubility, which gives one flexibility in choosing the solvent based on the drug's solubility.
- Polyvinyl Alcohol (PVA)** - produced by hydrolyzing the acetate groups in polyvinyl acetate after the vinyl acetate monomer is polymerized to create polyvinyl acetate. In addition to being fragile and challenging to handle, the films biodegrade slowly, especially in anaerobic environments.

Plasticizers^[1,21,31]

By including plasticizer in the formulations, the mechanical characteristics, such as the tensile strength and % elongation of films, are enhanced. Plasticizer typically has a concentration of 0% to 20% w/w. An inadequate concentration of plasticizers in ODF formulations can cause the film to peel, crack, or strip.

The plasticizers that are frequently utilized when preparing ODF are as follows:

- Glycerine
- Polyethylene Glycol
- Propylene Glycol
- Dimethyl phthalate
- Dibutyl phthalate
- Triacetin
- Citrate Ether
- Triethyl citrate

Sweetening Agent^[1,21]

The concentration of sweeteners used is 3-6% w/w. The pharmaceutical industry has employed fructose, glucose, maltose, sucrose, and dextrose as sweeteners. Sorbitol, mannitol, and maltitol are examples of polyhydric alcohols that have a pleasant mouthfeel and a cooling effect. An option are artificial sweeteners like aspartame, cyclamate, and saccharin. However, the harsh aftertaste left by these artificial sweeteners can be mitigated by combining or blending natural and artificial sweeteners. Some of the sweeteners that are frequently used in ODFs are listed below:

Natural Sweeteners	Glucose, Fructose, Dextrose , Sucrose, Isomaltose
Artificial Sweeteners	Acesulfame-K, Sucralose,Aspartame, Neotame, Saccharin

Flavouring Agent^[21]

In ODF formulations, flavors are added at a concentration of less than 10% w/w. Elderly people typically like flavors like mint or orange, whereas younger people like fruit punch or raspberry. ODF formulations often rely on the initial flavor quality, which is detected in the first few seconds after consumption, and consequently the formulation's aftertaste, which lingers for at least ten minutes.

Saliva Stimulating Agent^[31-33]

These substances are meant to stimulate salivation, which aids in the breakdown of the oral film. It contains acids such as malic, tartaric, ascorbic, and citric acids. usually utilized at a concentration of 2–6% weight per weight of the film.

Taste Masking Agent^[34]

The film's taste masking agent concentration is based on how bitter the medicine is. Glyceryl palmitostearate, Eudragit EPO, and Glyceryl monostearate are a few examples of flavor masking agents.

VIII. METHODS OF MANUFACTURING^[1,21,34]

Following are the methods used in preparation of orally disintegrating film:

Casting Method	a) Solvent Casting b) Semi solid Casting
Extrusion Method	a) Hot Melt Extrusion
Rolling Method	a) Using a roller
Printing Method	a) Inkjet Printing b) Flexographic Printing

Solvent Casting Method^[1,21]

The method most frequently employed to prepare ODFs is solvent-casting. Excipients and APIs in an aqueous or hydroalcoholic solution are poured onto a surface, let to dry, and then sliced into the required size. This process involves vacuum-pressurizing the suspension of polymers, plasticizers, and APIs to release trapped air bubbles before adding it to a mold, like a Teflon plate or petri dish, and drying it.

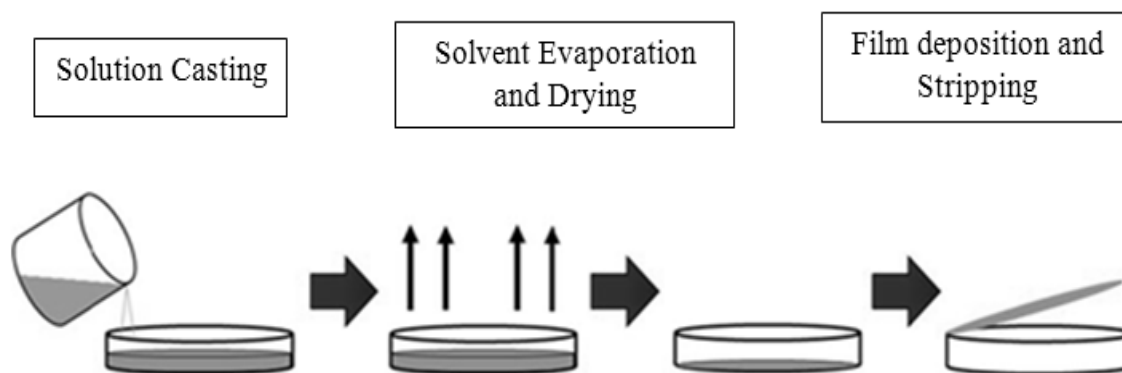


Figure: Solvent Casting Method^[37]

Semisolid Casting Method^[44,45]

Two primary polymers, such as hydrophilic and hydrophobic polymers, are needed for this technique. First, a solution made of a polymer that forms a film in water is made. A solution of acid-insoluble polymers (such as cellulose acetate phthalate or cellulose acetate butyrate) in ammonium or sodium hydroxide is combined with the gel mass of the solution. A 1:4 ratio must be present in the solution between the soluble film-forming polymer and the

acid-insoluble polymer. Ultimately, drums with heat control are used to cast the gel mass. The film has a thickness of between 0.015 and 0.5 inches.

Hot Melt Extrusion (HME)^[36,39-43]

Granules, sustained-release pills, and transdermal and transmucosal drug delivery systems are typically made with HME. Using API-polymer combinations, HME is a continuous processing technology used in pharmaceuticals to obtain the required drug release patterns. For this procedure, temperature, speed, feeding rate, and pressure conditions are essential process parameters. HME technologies offer several benefits, including ease of shape, reduced number of operating units, minimal product waste, capacity to scale up, appropriateness for pharmaceuticals sensitive to moisture, and effective solubility augmentation for poorly soluble APIs. HME techniques are expensive and need specialized tools.

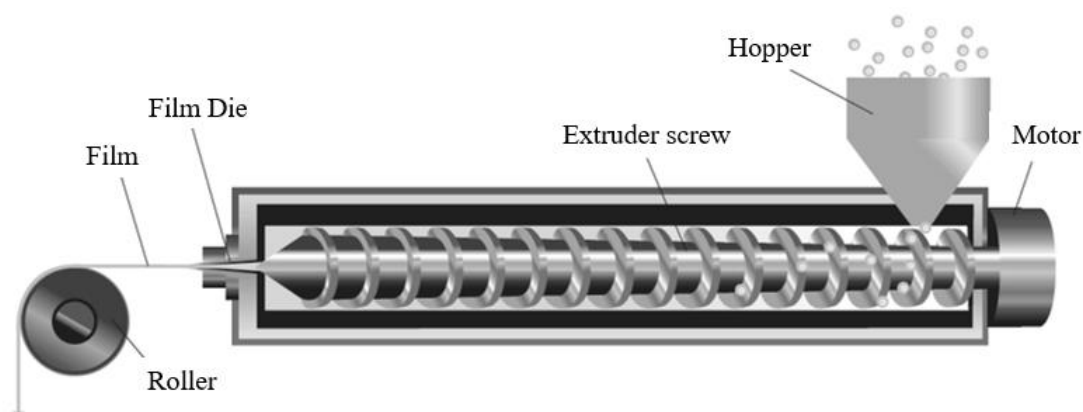


Figure: Hot Melt Extrusion^[37,38]

Rolling Method^[35]

This process starts with the preparation of a suspension made of water, alcohol and water mixture, film-forming polymers, and other excipients. The suspension is fed through a metering roller, after which a metering pump and control valve regulate how much suspension reaches the mixers. In a mixer, the suspension and APIs are combined to create a homogenous matrix that is delivered by the metering pumps. The metering roller measures the film's thickness and applies it using the applicator roller. The film is finally produced on the substrate and removed by the backing roller. In the absence of heat or external air currents on the film's top surface, the wet film is subsequently dried with the aid of controlled bottom drying.

Printing Method^[46,47]

Unstable APIs could react negatively to drying and mixing. In solvent-casting and hot-melt extrusion, the medication must be combined with the polymer before the film is formed. Depending on the physicochemical characteristics of the API, this could result in modifications to the mechanical properties of films. By printing APIs onto a substrate film layer, the printing process functions as a substitute. The low manufacturing speed of this approach limits its capacity to guarantee a homogenous distribution and improve API

stability. While inkjet printing can distribute strong or low-dose APIs precisely, it is not a good option for high-throughput manufacturing. When printing flexographically, an API-infused ink is first stained with a roller before being moved to a printing cylinder.

IX. CRITICAL QUALITY ATTRIBUTES^[8]

- 1. Stability Studies:** Oral films have been stored for a duration of 12 months under controlled settings of 25°C/60% RH and 40°C/75%, in accordance with ICH recommendations. Oral films should be assessed for their morphological characteristics, mass thickness, film thickness reduction, tensile characteristics, water content, and dissolving behavior under these storage circumstances.
- 2. Drug Content And Content Uniformity:** The drug content is ascertained using the standard assay procedures specified for that particular API. The calculation of each film's API content yields the content uniformity. The range of content homogeneity is 85–115%.
- 3. Dissolution Test:** It is possible to conduct dissolution tests with a typical paddle or basket device. The high dosage of the active substance and the sink condition determine the dissolving medium to use. The paddle apparatus occasionally has trouble getting the strip to float on the dissolving media during the dissolution test.
- 4. Disintegration Time:** Fast disintegrating oral film has a maximum disintegration time of 30 seconds or less. Although there isn't an official guideline yet, this could serve as a qualitative guideline for quality control testing. Oral strips typically dissolve in 5 to 30 seconds.
- 5. Organoleptic Evaluation:** People accept things that have flavor and sweetness characteristics. Specialized controlled human tasting panels are employed to evaluate products. To achieve this, modified pharmacopoeial procedures, taste sensors, and specifically constructed equipment are employed in vitro. Electronic tongue measurements are used in experiments to quantify the sweetness level in taste-making formulations.^[48, 49]
- 6. Physical Strength^[50-52]:** The appropriate physical strength of the oral film is one of the most evident critical quality attribute and also have suitable mechanical properties so it can be easily packaged, handled and manufactured without damage and break. The main properties that should be tested are Young's modulus, Tensile strength and elongation at break. Depending on the polymer matrix and method of manufacture the appropriate value for the mechanical strength is very significant. The oral film should not be too flexible so that it expands easily and deform during cutting or packaging process and it should also be malleable so that it can be handled without break. It should have enough tensile so it can be easily put out from the pouch, peeled from the release liner, rolled up after casting, but in limit because that may create difficulties in cutting process.
- 7. Physical Appearance:** Size and shape should be carefully considered and chosen based on the strength and application site. This is significant since there was less surface area available for adhesion in sublingual formulation. Comparable to buccal film, which is

inserted into the mouth and left there for an extended amount of time while maintaining the right size for patient comfort.

X. CONCLUSION

The current chapter demonstrates that orally disintegrating film is a modern approach in drug delivery system. Their acceptance and patient compliance has increased without choking fear linked to improved safety and effectiveness as compared to traditional dosing forms. The primary aim behind the development of ODFs was to address the challenge that patients with dysphagia who are pediatric, geriatric, or psychiatric face when swallowing standard oral dose forms. Oral films are now extensively accessible for conditions including hypertension, acidity, allergies, discomfort, etc., demonstrating their significance. One of the main benefit of this dosage form is that it can be administered without the need for water, which satisfies the needs of the target demographic who prefers convenience in medication administration.

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