CHAPTER TITLE

**ORALLY DISINTEGRATING FILM – A MODERN APPROACH IN DRUG DELIVERY SYSTEM**

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**Topic Covered**

1. Introduction
2. Anatomy and physiology of oral mucosa
3. Drug delivery through oral mucosa
4. Classification of oral films
5. Advantages of thin film over conventional dosage form
6. Clinical advantages of thin film
7. Major limitations of thin film
8. Components of film
9. Active Pharmaceutical Ingredient (API)
10. Polymer
11. Plasticizer
12. Sweetening agent
13. Flavouring agent
14. Coloring agent
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16. Taste masking agent
17. Methods of manufacturing
18. Critical quality attributes
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**ABSTRACT**

Innovative drug delivery methods have drawn more attention in recent years in an effort to boost patient compliance, safety, and effectiveness. The search and creation of novel chemical entities is a costly 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. Oral disintegrating film or strips containing water dissolving polymer retain the dosage form to be quickly hydrated by saliva, disintegrate within a few seconds and releases the medication in oromucosal cavity when placed in mouth. This chapter gives a detail of merits, demerits of orally disintegrating film, components, manufacturing process and critical quality attributes.

**INTRODUCTION(1,2)**

Oral route the most preferred routes of drug administration owing to its safety, ease of administration, and acceptability by patients. About 60% of conventional dosage forms are available in oral solid dosage forms. But due to low bioavailability, longer onset of action, and dysphagia, the manufacturer went for the parenterals and liquid dosage forms. But the liquid dosage forms (syrup, suspension, emulsion, etc.) have the problem of accurate dosing and parenterals are painful drug delivery systems, occurred in the liquid dosage forms resulting in patient non-compliance.

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 wthin 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.

**THE ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA(3)**

The oral mucosa is the mucous membrane lining the inside of the mouth. It comprises of stratified squamous epithelium, termed "oral epithelium", and an underlying connective tissue termed lamina propria. Oral mucosa is divided into three main categories based on function and histology:

1. Lining mucosa, nonkeratinized stratified squamous epithelium, found almost everywhere else in the oral cavity, including the:

(a) Alveolar mucosa, the lining between the buccal and labial mucosae. It is bright red, shiny, and smooth with many blood vessels, and is not connected to underlying tissue by rete pegs.

(b) Buccal mucosa, the inside lining of the cheeks and floor of the mouth; part of the lining mucosa.

(c) Labial mucosa, the inside lining of the lips; part of the lining mucosa.

2. Masticatory mucosa, keratinized stratified squamous epithelium, found on the dorsum of the tongue, hard palate, and attached gingiva.

3. Specialized mucosa, specifically found in the regions of the taste buds on lingual papillae on the dorsal surface of the tongue; contains nerve endings for general sensory reception and taste perception.

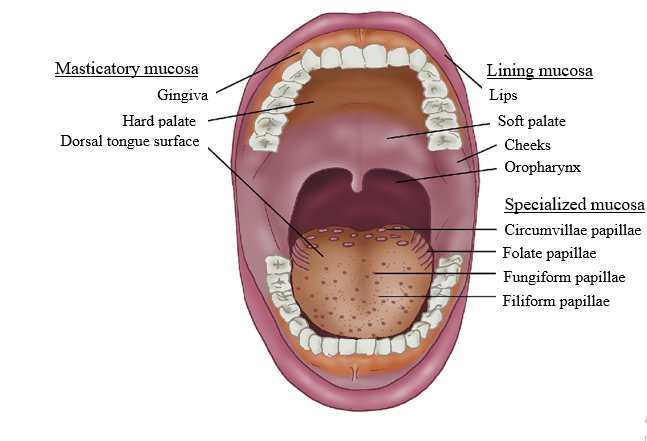


Figure - Oral Mucosa(6)

There are five tastes located on different receptors on the tongue, sensations for sweet are located at the tip of the tongue, and sensations for sour are located at the sides of the tongue whereas bitterness at the back of the tongue and salty sensations are located at the sides and tip of the tongue. These above taste receptors bind molecules down by saliva and transmit electrical impulses by the 7th, 9th and 10th cranial nerves to these areas of the brain that participate in the perception of taste.

The enzymes and the mouth's moist environment within its secretions help to soften food, facilitating, swallowing, and beginning the process of digestion. The salivary glands secrete mucin as part of saliva. Saliva pH ranges from 6.8 to 7. The permeability of buccal mucosa is found to be 4000 times greater than skin.

**DRUG DELIVERY THROUGH ORAL MUCOSA(4,5)**

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

1. Local Drug Delivery
2. Systemic Drug Delivery

**SYSTEMIC DRUG DELIVERY**

**LOCAL DRUG DELIVERY**

* **GINGIVAL MUCOSA**
* **PALATAL MUCOSA**
* **BUCCAL MUCOSA**
* **SUBLINGUAL MUCOSA**
* **ABSORPTION THROUGH GIT**

**NON KERATINIZED MUCOSA**

**KERATINIZED MUCOSA**

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 occuring at the gingiva or palate.

**Sublingual drug delivery** - the systemic delivery of drugs through the mucosa lining the floor of mouth. This is generally used for the systemic delivery of drugs in treating acute disorders. The sublingual mucosa is more permeable and thinner as compared to the buccal mucosa, making it a feasible site if a rapid onset is desired.

**Buccal drug delivery -** drug delivery via the buccal mucosa lining. As the buccal mucosa is considerably less permeable than the sublingual mucosa, and it is not able to provide the rapid onset of absorption. Thus, buccal mucosa constitutes a preferred route for the systemic treatment of chronic disorders when the sustained delivery of systemically acting drugs is required.

**CLASSIFICATION OF ORAL FILMS(7,8)**

There are three types of oral films:

1. Flash release

2. Mucoadhesive melt away wafer

3. Mucoadhesive sustained release wafers

|  |  |  |  |
| --- | --- | --- | --- |
| **Properties** | **Flash release** | **Mucoadhesive Melt away wafer** | **Mucoadhesive Sustained release wafers** |
| **Structure** | Film:single layer | Single or  multilayer system | Multilayer system |
| **Excipient** | 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 |
| **Application** | Tongue (upper palate) | Gingival or buccal region | Gingival (other region in the oral  cavity |
| **Dissolution** | Maximum 60 sec | Disintegration in a  few minutes, forming gel | Maximum 8-10 hours |
| **Site of action** | Systemic or local | Systemic or local | Systemic or local |

**ADVANTAGES OF THIN FILM OVER CONVENTIONAL DOSAGE FORM(9-13)**

* Dissolution occurs rapidly as compared to conventional dosage form.
* It is less friable and easy to carry dosage form than orally disintegrating tablet which requires special packaging.
* Advantageous over liquid dosage form that has poor stability and need of care for measuring amount and shaking the bottle every time before use owing to its less acceptability to patients.
* Conventional opthalmic dosage forms like solution and eye drops have a limitation in providing high ocular drug bioavailability and sustain duration of action.
* Opthalmic film can be the alternative to improve drug delivery to eye.

**CLINICAL ADVANTAGES OF THIN FILM(14-16)**

* Due to its appellative form and ease of administration ,patients show preference towards thin film.
* Easy administration and avoid the risk of choking or suffocation, makes it suitable for pediatric, geriatric, psychiatric patient. Thus ensuring patient safety.
* Ophthalmic films enhance the retention time of a drug and thereby, improves the absorption of the drug from the anterior segment of the eye.
* Beneficial for bedridden and non-cooperative patients.
* Useful in cases where a rapid onset of action is required as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma.

**MAJOR LIMITATIONS OF THIN FILM(15-19)**

* Low drug loading capacity makes it limitation for a less potent drug given at high dose.
* Due to its hygroscopic nature special care is to be taken during storage.
* Using a combination of drug is difficult task because it will hinder both disintegration time and dissolution rate.
* The difficulty of obtaining high degree of accuracy with respect to the amount of drug in individual unit dose of the film can result into therapeutic failure, non- reproducible effects and sometimes toxic effects to the patient.
* Preparation requires excess time for drying.

**COMPONENTS OF FILM**

The ingredients used in formulation of orally disintegrating film should be generally reccomended 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)**

Active pharmaceutical ingredient can be incorporated up to 5-30%w/w along with other excipients. APIs can be milled, micronized or loaded in the form of nanocrystals or particles on the basis of desired release profile. Bitter drugs taste is required to be masked before incorporating APIs in the film.(20) Different techniques are used to enhance the taste but amongst them the simplest method includes mixing and co-processing of bitter testing API with excipient with good pleasant taste called as obscuration technique**.**

**POLYMERS(8, 21-30)**

The most important step in the development of ODFs is the selection of the polymer or polymer mixtures as the drug-release matrices are the most important component of the ODFs and helps to achieve desirable properties such as disintegration time, drug loading capacity, mechanical strength, and drug release profile.The polymers should be non-toxic, non-irritant, and of high purity,good wetting and spreadability,sufficient feel, and good shear and tensile strength, should be commercially available and inexpensive, should have a good shelf life, and not cause infections in the oral mucosa.

|  |  |
| --- | --- |
| **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 pyrollidone |

* **Pullulan** - Produced by Aureobasidium pullulans, it is a water-soluble glucan gum made of maltotriose units and a neutral polysaccharide with low oxygen permeability. Pullulan has excellent film-forming properties and therefore the resulting films are colorless, soluble, odorless, transparent, flexible, tasteless, nontoxic, heat-sealable, and a barrier to antioxidants.
* **Gelatin** - Gelatin is produced by the hydrolysis or thermal degradation of collagen, and is majorly extracted from the bones, hide, and connective tissues of porcine or bovine sources. Gelatin-based films are flexible, transparent, and have unique properties, arising from their low melting point, and biodegradable and edible nature. Gelatin film are unexpensive.
* **Chitosan -** Chitosan films have low oxygen permeability, good biocompatibility, biodegradability and favorable toxicological properties. The antibacterial and antifungal activity of chitosan-based films had the ability to extend drug shelf life.
* **Hydroxy Propyl Methyl Cellulose** (HPMC) - Composed of 19–30% methoxyl (–OCH3) groups and 3–12% of hydroxypropyl (–OCH2CHOHCH3) groups. Grade letters such as E, K, J, and F represent the classified degree of hydroxypropyl and methoxyl substitution and molar substitution. It is soluble in cold water and forms a hydrocolloid, whereas almost insoluble in hot water, dehydrated alcohol, acetone, and toluene. It is commonly used as an excipient, coating agent, film former, viscosity modifier, and release controller resulting into superior film-forming capability and good biocompatibility and biodegradability.
* **Hydroxy Propyl Cellulose** (HPC)- A cellulose derivative in which some of the hydroxyl groups of the cellulose have been hydroxypropylated to form – OHCH-2CHOHCH3 groups. HPC is freely soluble in cold water and results in a smooth, clear, colloidal solution. In hot water, it is insoluble, but is soluble in many cold or hot polar organic solvents. HPC has been used as a film former due to its good film-forming ability with decent mechanical properties such as good carrying capacity, reasonable clarity, and moderate bioadhesion. An advantage of the HPC is the wide range of solubility, which allows flexibility in the selection of the solvent according to the drug solubility.
* **Polyvinyl Alcohol** (PVA) - Manufactured by the polymerization of the vinyl acetate monomer into polyvinyl acetate, followed by hydrolysis of the acetate groups of polyvinyl acetate.The films may be brittle and difficult to handle, and its biodegradation is a relatively slow process, particularly under anaerobic conditions.

**PLASTICIZERS(1,21,31)**

The mechanical properties such as tensile strength and percent elongation of films are improved by adding plasticizer to the formulations. The concentration of plasticizer generally ranges from 0% to 20% w/w. Inappropriate concentration of plasticizers within the ODF formulations may lead to cracking, stripping, peeling of film.

Following are the commonly used plasticizers in ODF preparation:

* Glycerine
* Polyethylene Glycol
* Propylene Glycol
* Dimethyl pthalate
* Dibutyl pthalate
* Triacetin
* Citrate Ether
* Triethyl citrate

**SWEETENING AGENT(1,21)**

Sweeteners are used at a concentration of 3–6% w/w. Sucrose, dextrose, fructose, glucose, and maltose have been used as sweeteners in pharmaceutical industry. Polyhydric alcohols like sorbitol, mannitol, and maltitol produce a good mouth feel and cooling sensation. Artificial sweeteners like saccharin, cyclamate, and aspartame are an alternative. But these artificial sweeteners gives a bitter aftertaste, which may be reduced by the mixing or blending of natural and artificial sweeteners. Following are some of the commonly used sweetening agents in ODFs:

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

**FLAVOURING AGENT(21)**

Flavours are added at a concentration that is less than 10% w/w in ODF formulations. The geriatric population usually prefers mint or orange flavors, whereas the younger generation favors fruit punch or raspberry flavors. ODF formulation usually depend upon the initial flavor quality which is perceived within the first few seconds after the product has been consumed and therefore the aftertaste of the formulation which lasts at least 10 min.

**SALIVA STIMULATING AGENT(31-33)**

These agents are used to increase the production of saliva which assists in the disintegration of the oral film. It include acids like citric acid, tartaric acid, ascorbic acid and malic acid. Generally, used in a concentration of 2-6% w/w of weight of the film.

**TASTE MASKING AGENT(34)**

Concentration of taste masking agent in the film depends on the bitterness of the drug. Some of the examples used as taste masking agents are Eudragit EPO and Glyceryl Monostearate, Glyceryl Palmitostearate, etc.

**METHODS OF MANUFACTURING(1,21,34)**

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

|  |  |
| --- | --- |
| **Casting Method** | 1. Solvent Casting 2. Semi solid Casting |
| **Extrusion Method** | 1. Hot Melt Extrusion |
| **Rolling Method** | 1. Using the roller |
| **Printing Method** | 1. Inkjet Printing 2. Flexographic Printing |

**SOLVENT CASTING METHOD(1,21)**

Solvent-casting is the most commonly used to prepare ODFs. An aqueous or hydroalcoholic solution of excipients and APIs are casted onto a surface, dried, and then cut into a desirable size. In this method, the suspension comprising of APIs, polymers, and plasticizers is placed in a vacuum to remove entrapped air bubbles and then introduced onto the mold such as a Teflon plate or petri dish, which is then dried.

Film deposition and Stripping

Solvent Evaporation and Drying

Solution Casting

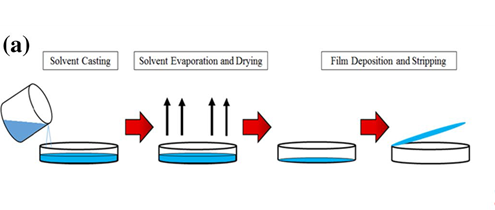


Figure – Solvent Casting Method(37)

**SEMISOLID CASTING METHOD(44,45)**

This method requires two main polymers like hydrophilic and hydrophobic polymers. Initially, a solution composed of a watersoluble film-forming polymer is prepared. The gel mass of the solution is mixed with a solution composed of acid-insoluble polymer (e.g.,cellulose acetate phthalate or cellulose acetate butyrate)in ammonium or sodium hydroxide. The ratio of solution of soluble film-forming polymer to acid-insoluble polymer must to be 1:4. Finally, the gel mass is casted using heat-controlled drums. The thickness of the film is about 0.015–0.5 inches.

**HOT MELT EXTRUSION (HME)(36,39-43)**

HME is generally used to prepare granules, sustained-release tablets, and transdermal and transmucosal drug delivery systems. HME is used pharmaceuticals utilizes a continuous processing technology that can achieve the desired drug release profiles by API-polymer mixtures. The critical process parameters of this method include temperature, speed, feeding rate, and pressure conditions. The HME methods have advantages like simplicity of shaping, fewer operation units, minimum product wastage, scale-up capabilities, suitability for moisture-sensitive drugs, and efficacy of solubility enhancement for poorly soluble APIs. HME methods are costly and require special equipment.

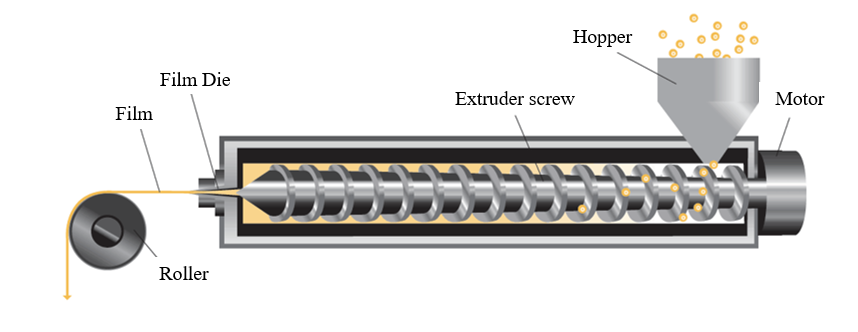


Figure – Hot Melt Extrusion(37,38)

**ROLLING METHOD(35)**

In this method, a suspension comprising of film-forming polymers, water, a mixture of water and alcohol, and other excipients is initially prepared. The suspensionis passed through a metering roller, where the amount of suspension is controlled through a metering pump and control valve to the mixers. The APIs are mixed with the suspension in a mixer to provide a uniform matrix through the metering pumps. The thickness of the film is determined by metering roller and applies it with the applicator roller. Lastly the film is formed on the substrate and carried away through the backing roller. The wet film is then dried with the help of controlled bottom drying, in the absence of external air currents or heat on top surface of the film.

**PRINTING METHOD(46,47)**

APIs which are unstable in nature may be sensitive to mixing and drying. The drug is required to be mixed with the polymer in case of solvent-casting and hot-melt extrusion prior to forming the film. This may lead to changes in the mechanical properties of films depending on the physicochemical properties of the API. The printing method serves as an alternative way by printing APIs onto a substrate film layer. This method ensures a homogeneous distribution, and increases stability of the API, this methods are limited by a low production speed. Inkjet Printing can precisely spread potent or low-dose APIs, but not suitable for high-throughput production. In Flexographic printing, the ink with API is stained with a roller and then transferred to a printing cylinder which prints the drugfree film.

**CRITICAL QUALITY ATTRIBUTES(8)**

**STABILITY STUDIES**

According to ICH guidelines oral films have been stored under controlled conditions of 25°C/60% RH and 40°C/75% over a period of 12 months. Under this storage conditions, oral films should be evaluated for their morphological properties, mass thickness, reduction of film thickness, tensile properties, water content and dissolution behaviour.

**DRUG CONTENT AND CONTENT UNIFORMITY**

The standard assay methods described for the specific API determine the drug content. Content uniformity is determined by calculating the API content in individual film. Content uniformity is limited to 85-115%.

**DISSOLUTION TEST**

Dissolution testing can be performed by using standard paddle or basket apparatus. The choice of dissolution media depends on the sink condition and high dose of active ingredient. The paddle apparatus sometimes dissolution test tends to have problem of strip to float on dissolution medium.

**DISINTEGRATION TIME**

The disintegrating time for fast disintegrating oral film have a limit of 30 seconds or less can be employed. But yet no official guideline is present, this may be used as a qualitative guideline for quality control test. Usually, disintegration time for oral strip is 5-30 seconds.

**ORGANOLEPTIC EVALUATION**

The products that possess features of sweetness and flavor are accepted by people. For product evaluation special controlled human taste panels are used. For this purpose, invitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are used. To determine the sweetness level in taste making formulation, experiments by using electronic tongue measurements are performed.(48,49)

**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, pealed from the release liner, rolled up after casting, but in limit because that may create difficulties in cutting process.

**PHYSICAL APPEARANCE**

Depending on the strength and application site the size and shape should be carefully studied and selected . This is important in sublingual formulation in which it had a smaller available area to adhere. Similar in case of buccal film which placed in mouth for long period of time with suitable dimension for patient comfort.

**CONCLUSION**

The current chapter demonstrates that orally disintegrating film is a novel approach in modern 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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1. Mouth Dissolving Films: Innovative Vehicle for Oral Drug Delivery

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