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ADVANCEMENTS IN DRUG DELIVERY: A COMPREHENSIVE REVIEW OF ORALLY DISINTEGRATING FILMS (ODF'S)

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Abstract:

Orally disintegrating films (ODFs) have garnered significant attention in recent years as a promising drug delivery system. This comprehensive review explores the formulation, advantages, challenges, and future prospects of ODFs in pharmaceutical and Nutraceutical applications. Key features such as composition, formulation techniques, manufacturing considerations, taste-masking and Evaluation parameters are discussed. The strengths and weaknesses of ODFs are analyzed, along with potential solutions to address formulation complexity and stability challenges. The review concludes with insights into ongoing research efforts and the potential impact of ODFs on drug delivery innovation.

Keywords: Orally disintegrating films, drug delivery, formulation, Advantages,

1. INTRODUCTION [1][2][3][4][5]

The field of drug delivery has witnessed remarkable advancements aimed at enhancing therapeutic efficacy, patient compliance, and convenience. Orally disintegrating films (ODFs) have emerged as a promising dosage form offering numerous advantages over conventional oral dosage forms. This review provides a comprehensive overview of ODFs, including their formulation, advantages, challenges, and future prospects in pharmaceutical and Nutraceutical applications applications.

Orally disintegrating films (ODFs) are thin, flexible films containing active pharmaceutical ingredients (APIs) that dissolve or disintegrate rapidly upon contact with saliva, allowing for quick absorption through the oral mucosa. ODFs address the need for patient-friendly dosage forms, particularly for pediatric, geriatric, and dysphagia patients. The development of ODFs has been driven by the desire to improve patient compliance, enhance drug bioavailability, and provide a convenient dosing option for individuals with swallowing difficulties.

Oral route drug delivery is one of the most preferred routes to administer a drug as it is cost effective, ease of manufacturing, more convenient which leads to patient compliance. Sublingual route is a promising route which

gives faster onset of action with direct absorption drug in systemic circulation. It provides better utilization of drug and enhance the efficacy and activity of drug at site of action. It is beneficial in the patient having difficulty in swallowing of tablets or capsules. It may formulate for the diseases such as; sudden episodes of allergic reactions, motion sickness, heart attack, allergic rhinitis and CNS disorders. Sublingual film is putted beneath the tongue.

The Absorption of the drug occurs in this way:

Sublingual > Buccal > Gingival > Palatal

1.1 Classification of Orally disintegrating films (ODF'S) [6]

1. Flash release.
2. Mucoadhesive melt-away wafer.
3. Mucoadhesive sustained release wafers.

Properties	**Flash release**	**Mucoadhesive melt-away wafers**	**Mucoadhesive sustained release wafers**
Area (cm^2)	2-8	2-7	2-4
Thickness (µm)	20-70	50-500	50-250
Structure	Single layer	Single or multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low/nonsoluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspended and/or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival, (another region in the oral cavity)
Dissolution	60 sec	In few minutes forming gel	Maximum 8-10Hr
Site of action	Systemic or local	Systemic or local	Systemic or local

Table 1 Types and Properties of Different Orally disintegrating films

1.2 Special features of Orally disintegrating films [7]

- Film should be thin and elegant.
- Available in various size and shapes.
- Unobstructive.
- It should adhere to the oral cavity easily.
- Should processes fast disintegration without water.
- Rapid release.

1.3 Advantages of Orally disintegrating films [8]

- Convenient dosing.
- No water needed.
- No risk of chocking.
- Taste masking.
- Enhanced stability.
- Improved patient compliance.

- The drug enters the systemic circulation with reduced hepatic first pass effect.
- Site specific and local action.
- Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
- Dose accuracy in comparison to syrup.

1.4 Disadvantages of Orally disintegrating films

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

1.5 Ideal Characteristics of a Suitable Drug Candidate

- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.

1.6 Standard Composition of Mouth Dissolving Strip [9]

- Mouth Dissolving Strip is a thin film with an area of 1-20 cm^2 (depends on dose and drug loading) containing drug.
- Drugs can be loaded up to a single dose of 30 mg.

Ingredients	Amount	Examples
Drug	5-10 %w/w	• Antiallergic, • antiemetic, • antiepileptic, • antimigrant
Water soluble polymer	45 %w/w	• HPMC E5, E15 and E50, • Methyl cellulose A-3, A-6, A-15, • Pullulan, • PVP K-90, • Sodium alginate, etc.
Plasticizer	0-20 %w/w	• Glycerol Anhydrous, • Polyethylene glycol, etc.
Surfactants	q.s.	• Sodium lauryl sulfate, • Tween, • Benzalkonium chloride, etc.
Sweetening agents	3-6 %w/w	• Saccharin, • Aspartame, • Sucralose, • Neotame, etc.
Saliva stimulating agents	2-6 %w/w	• Citric acid, • Tartaric acid, • Ascorbic acid, etc.

Fillers, colors, flavors	q.s.	• FD and C colors, US FDA approved flavors.

Table 2 Standard Composition of Orally disintegrating films

1.7 Ideal properties of film forming polymers [10]

- Nontoxic and nonirritant.
- Devoid of leachable impurities.
- Should not retard disintegration time of film.
- Tasteless.
- Should have good wetting and spread ability property.
- Should have sufficient peel, shear, and tensile strength.
- Readily available.
- Inexpensive.
- Sufficient shelf life.
- Should not aid in causing secondary infections in oral mucosa.

2. Various Method of Preparation of Orally disintegrating films [11]

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

2.1 Solvent Casting Method [12]

- In this method, firstly the water-soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C.
- All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately.
- Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm.
- The obtained solution is incorporated with the API dissolved in suitable solvent.
- The entrapped air is removed by vacuum.
- The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

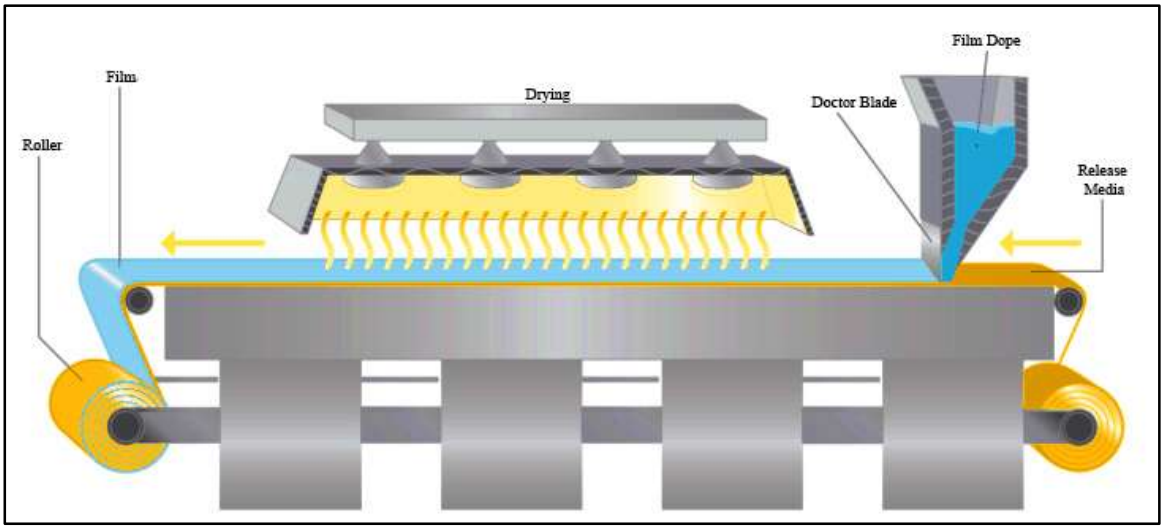

Figure 1 Diagram of Solvent Casting Film System

2.2 Hot-Melt Extrusion

- In hot melt extrusion method, the initial mass is formed with the help of carriers.
- To form initial mass, the drug is mixed with carriers and a solid mass is obtained and dried.
- Then dried granular material is introduced into the extruder.
- The extruder is divided into four zones having following degrees of temperature: 800 (zone 1), 1150 (zone 2), 1000 (zone 3), and 650°C (zone 4).
- The speed of extruder screw speed should be set at 15 rpm in order to process the granules inside the barrel of extruder for approximately 3-4 min so that mass should be properly melted.
- The extrudate (T = 650°C) obtained is then pressed into a cylindrical calendar in order to obtain a film.
- There are certain benefits of hot melt extrusion:
    - Fewer operation units, minimum product wastage, possibility to scale up, an anhydrous process, absence of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix, and better content uniformity.

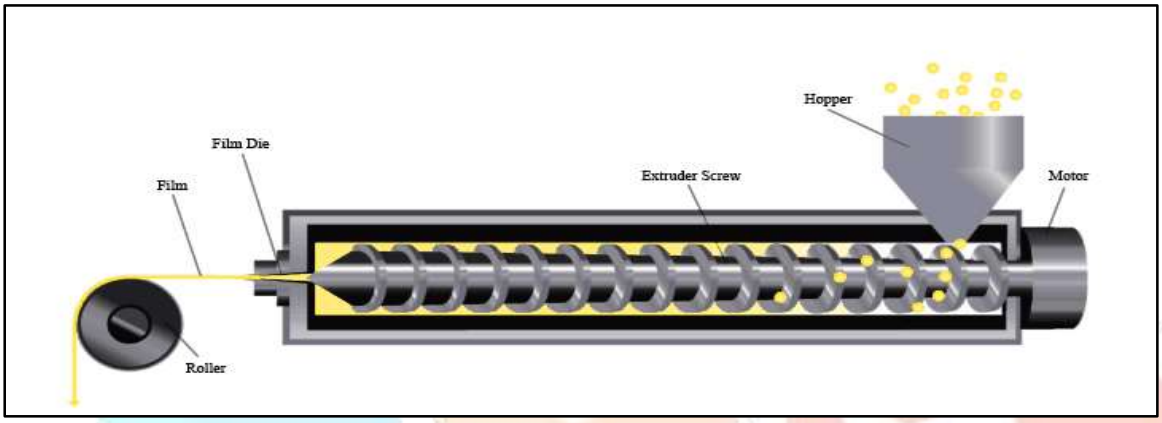

Figure 2 Hot-melt Extrusion System

2.3 Semi-solid casting

- This method is mostly preferred when film ingredient involves acid insoluble polymer.
- In this firstly, the water-soluble polymers are dissolved in water.
- The obtained solution is added to the acid insoluble polymer solution which is separately formed.
- Both the solutions are mixed properly.
- After mixing the two solutions, appropriate amount of plasticizer is added to the obtained final solution so that gel's mass can be obtained.
- At last, the gel mass is casted onto the films or ribbons using heat-controlled drums.
- The thickness of the film should be about 0.015-0.05 inches.
- The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Examples of acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate.

2.4 Rolling

- In rolling method, both the drug solution and film forming polymer solution are mixed thoroughly and the resultant solution or suspension is subjected to the roller.
- The solution or suspension should have specific rheological consideration.
- The film is dried on rollers and cut into desired shapes and sizes.

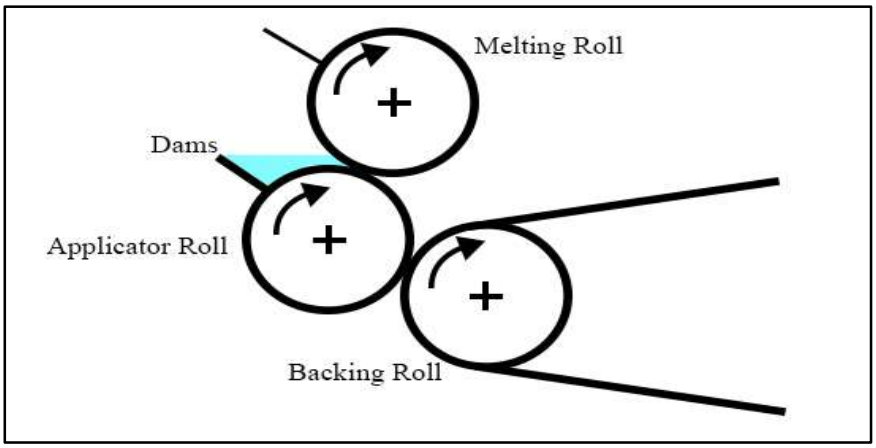

Figure 3 Rolling System

3. Evaluation of Orally disintegrating films [13]

3.1 Thickness

- The thickness of film is measured by digital Thickness meter micrometer screw gauge or calibrated digital Vernier Calipers.
- The thickness of film should be in range 5-200 μm.
- The thickness should be evaluated at five different locations (four corners and one at center) and it is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film.

Figure 4 Digital Thickness meter, Digital Vernier Calipers and Micrometer Screw Gauge Respectively

3.2 Dryness/ tack test

- In all there have been eight stages identified for film drying and these are 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.
- Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with strip.

3.3 Tensile Strength

- Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of strip as given in the equation below:
- Tensile strength = Load at failure × 100/Strip thickness × Strip width

3.4 Percent elongation

- When stress is applied on a film (2 × 2 cm2) sample it gets stretched, this is referred to strain.
- Strain is basically the deformation of strip before it gets broken due to stress.
- It is measured by using Hounsfield universal testing machine.
- Generally, elongation of strip increases as the plasticizer content increases. It is calculated by the formula: % Elongation = Increase in length of strip × 100/Initial length of strip

Figure 5 Hounsfield universal testing machine

3.5 Tear resistance

- Tear resistance is the resistance which a film offers when some load or force is applied on the film specimen.
- The load mainly applied is of very low rate 51 mm/min.
- The unit of tear resistance is Newton or pounds-force.
- In other words, it is the maximum force required to tear the specimen.

3.6 Folding Endurance

- Folding endurance gives the brittleness of a film.
- The method followed to determine endurance value is that the film specimen (2 × 2 cm2) is repeatedly folded at the same place until it breaks or a visible crack is observed.
- The number of times the film is folded without breaking or without any visible crack is the calculated folding endurance value

3.7 In vitro disintegration test [14]

- Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva.
- For an Orally disintegrating films , the time of disintegration should be in range of 5-30 s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time.
- In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker.
- The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates.

3.8 In vitro dissolution studies

- Dissolution is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature, and solvent concentration.
- The standard basket or paddle apparatus described in any of the pharmacopoeia can be used for dissolution testing.
- The selection of dissolution medium will essentially depend as per the sink conditions and highest dose of API.
- The temperature of dissolution medium should be maintained at 37 ± 0.5°C and rpm at 50.
- When the paddle apparatus is employed, it has a disadvantage that oral films have a tendency to float over the dissolution medium.

3.9 Drug content uniformity [15]

- This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia.
- Content uniformity is determined by estimating the API content in individual strip.
- Limit of content uniformity is 85-115%

3.10 Organoleptic test [7]

- The desired organoleptic properties a fast dissolving formulation should have are color, flavor, and taste. As the formulation will disintegrate in the oral cavity so it should provide acceptable organoleptic palatable characteristics.
- Color makes a formulation acceptable among the patients and moreover oral films should have attractive color as they are administered to children. Hence, color of formulation should be uniform and attractive. Color can be evaluated by visual inspection.
- The other organoleptic property is the odor. The flavor used in the formulation should provide good odor to the formulation. The odor of the polymer, drug, and any other excipient should be masked with use of flavoring agent.
- Taste is also an important factor which has to be evaluated. To evaluate the taste, special human taste panels are used. Experiments using electronic tongue measurements have also been reported to distinguish between sweetness levels in taste masking formulation. In this liquid samples can be analyzed directly, whereas solid samples need to be dissolved in a suitable solvent before analyzing.

3.11 Surface pH test

- The surface pH of fast dissolving strip can cause side effects to the oral mucosa, so it is necessary to evaluate the surface pH of film.
- The surface pH of film should be 7 or close to neutral. For this purpose, a combined pH electrode can be used. With the help of water, OS was made slightly wet and the pH was measured by bringing electrode in contact with surface of oral film.
- This study should be done on at least six films of each formulation and their mean ± SD can be calculated.
- In another method to determine the surface pH, the films are placed on the 1.5%w/v agar gel and then the pH paper are placed on the film, change in color of pH paper gives surface pH of the film.

3.12 Contact angle

- Contact angle measurement predicts the wetting behavior, disintegration time, and dissolution of oral film.
- These measurements are performed with help of goniometer (AB Lorentzen and Wettre, Germany) and the measurements should be done at room temperature.
- The water used to determine contact angle should be double distilled water. A drop of double distilled water is placed on the surface of dry film.
- Images of water droplet are recorded within 10 s of deposition by means of digital camera. Digital pictures can be analyzed by imageJ 1.28v software (NIH, USA) for angle determination.

3.13 Transparency

- To determine transparency of oral film, a simple ultraviolet (UV) spectrophotometer can be used. The film specimen is placed on the internal side of spectrophotometer cell. The transparency of films is calculated as follows:
- Transparency = (log T600)/b = −€c
- Where T600 is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

3.14 Scanning electron microscopy

- To study the surface morphology of film between different excipients and drug scanning, electron microscopy can be used.
- The film sample should be placed in sample holder and at ×1000 magnification, various photomicrographs can be taken using tungsten filament as an electron source.

3.15 Permeation studies [16]

- Even though permeability of oral mucosa is 4-1000 times greater than that of skin, permeation studies should be carried out.
- To study the permeability, modified Franz diffusion cell can be used along with porcine buccal mucosa.
- The Franz diffusion cell consists of a donor and a receptor compartment. In between the two compartments, mucosa is mounted and the size of the mucosa should be of the same size as that of the head of receptor compartment. The receptor compartment is filled with buffer and maintained at 37 ± 0.2°C and to maintain thermodynamics a magnetic bead stirring at a speed of 50 rpm is used.
- A film specimen moistened with a few drops of simulated saliva should be kept in contact with mucosal surface. The donor compartment should consist of 1 ml simulated saliva fluid of pH 6.8.
- At particular interval, samples are withdrawn and replaced by same amount of fresh medium. By suitable analytical method, percentage of drug permeated can be determined.

3.16 Percentage moisture loss

- To determine percentage moisture loss films of area 2 × 2 cm2 are cut and weighed accurately on an electronic balance. After weighing, the films were kept in desiccators containing fused anhydrous calcium chloride. The films should be kept for 72 h in the desiccator.
- After 72 h, they are taken out and again weighed and the percentage moisture loss of films was measured by using the formula:
- Percent moisture loss = (Initial weight − Final weight)/Initial weight × 100
- The percentage moisture loss studies are done to determine physical stability and integrity of the film.

3.17 Determination of % yield of Strips

- Percentage yield of strips can be calculated by the following formula:
  % yield = Mass of the strips obtained/Total weight of drug and polymer × 100

3.18 Stability study [17]

- Stability study should be carried out according to the International Conference on Harmonization (ICH) guidelines.
- The prepared formulation was wrapped in a special way. Firstly, it was wrapped in a butter paper then above it an aluminum foil was wrapped and the packing should be placed in an aluminum pouch and make it heat sealed.
- The storage conditions at which formulations are kept should be 40°C/75% relative humidity (RH). After 6 months, the films were evaluated for drug content, disintegration time, and physical appearance observation.

4. Storage and packaging of Orally disintegrating films [18]

- Fast dissolving strips can be packed using single pouches, blister card with multiple units, multiple-unit dispenser, and continuous roll dispenser.
- There are certain patented packaging systems for fast dissolving films such as Rapidcard by Labtec and Core-peel by Amcor flexible.
- The rapid card is of same size as a credit card and holds three films on each side. Every dose can be taken out individually.

5.Conclusion

Orally disintegrating films (ODFs) represent a versatile and patient-friendly drug delivery system with numerous advantages over conventional dosage forms. Despite challenges in formulation and stability, ongoing research and innovation are poised to propel the development of ODFs and expand their applications in pharmaceuticals. This comprehensive review provides insights into the formulation, advantages, challenges, and future prospects of orally disintegrating films (ODFs) in drug delivery. By addressing key considerations and highlighting areas for future research, this review aims to contribute to the advancement of ODFs as a preferred dosage form in pharmaceutical applications.

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