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Beyond the Traditional Pill: Orodispersible Films as the Next Generation of Medication

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Abstract: Orodispersible films (ODFs) are thin, flexible, and water-soluble films that dissolve in the mouth within seconds, delivering medication or other active ingredients directly to the bloodstream. This article comprehensively covers various aspects related to orodispersible films (ODFs), including the preparation techniques, testing procedures, benefits, drawbacks, regulatory factors, and future considerations. Films can be manufactured by using Solvent casting, hot melt extrusion, freeze drying, spray casting, electrospinning, electro spraying, semisolid casting, rolling methods, etc. It provides a detailed analysis of the various techniques used for the preparation of ODFs, along with the testing procedures used to assess their quality, performance, and safety.

Keywords: Orodispersible film, solvent casting, hot melting extrusion, in-vitro dissolution study.

I. Introduction:

The most popular medication administration route is oral dosage forms because they are simple to use, have high patient satisfaction and compliance, need little in the way of aseptic settings, and may be developed in a wide range of methods. The development of orodispersible medication administration in recent years has provided patients who have trouble swallowing solid doses with an alternative to solid tablets and capsules. The danger of choking is reduced by using orodispersible films (ODFs), which are thin polymeric films that breakdown and release medications when put on the tongue or any other oral mucosal tissue. Orodispersible dosage forms offer the chance to cater to the unique requirements of a particular subpopulation of patients suffering from a variety of illnesses, the most pertinent of which are dysphagia, Parkinson's disease, psychosis, thyroid disorder, stroke, and multiple sclerosis Orodispersible films (ODFs) are a type of pharmaceutical dosage form composed of thin film sheets comprised of hydrophilic polymers. These films are intended to be administered onto the tongue or mucosal surfaces of the oral cavity, where they disintegrate rapidly upon contact with saliva. Orodispersible films (ODFs) are characterized as polymeric films that are comparable in size to postage stamps, with a thickness that typically ranges from 12 to 100 micrometers and a surface area ranging from 2 to 8 square centimeters. The literature often reports common dimensions for ODFs as being 3 by 2 square centimeters or 2 by 2 square centimeters.

Advantages:
1. Rapid Disintegration.
2. Improved Patient Compliance.
3. Accurate Dosing.
4. Taste-Masking.
5. Portable and Discreet.
6. Flexible Dosing.
7. Enhanced Bioavailability.
8. Improved Stability.
9. Reduced First-Pass Metabolism.
10. Customization and Personalization.

Disadvantages:
1. Limited Drug Loading.
2. Moisture Sensitivity.
3. Manufacturing Complexities.
4. Taste and Texture.
5. Fragility and Damage.
6. Higher Production Costs.
7. Drug-Drug Compatibility.
8. Regulatory Considerations.
9. Environmental Impact.
10. Limited Application.

Composition: The standard configuration of an oral dissolving film (ODF) encompasses an active

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pharmaceutical ingredient (API), which is a drug or active compound. It also comprises a film-forming polymer, a plasticizer agent to confer flexibility and improve mechanical characteristics, fillers, saliva-stimulating agents for heightened salivation and improved disintegration, taste-masking agents such as flavours and sweeteners to mask the bitter and unpleasant taste associated with numerous APIs, colouring agents to enhance consumer appeal of the film, as well as additional components like surfactants, enzyme inhibitors, stabilizers, and thickening agents.

1. Polymer: Film-forming polymers play a crucial role in the production of ODFs. Achieving an optimal balance between mechanical properties and disintegration time is a significant consideration in selecting the appropriate polymer type and concentration for ODF formulation. The identification of an optimal polymer remains a challenging task as it must possess the ability to rapidly disintegrate within the oral cavity while simultaneously offering mechanical durability for handling, packaging, and storage purposes.

a. Maltodextrin: Maltodextrin, a non-sweet nutritious oligosaccharide derived from starch hydrolysis, is widely used as a food additive. It is easily digestible and absorbed by the body. Commercially available as a white hygroscopic powder, maltodextrin consists of three to nineteen units of D-glucose, primarily linked by α-(1 → 4) glycosidic bonds. Maltodextrin possesses desirable properties such as film-forming ability, odorlessness, good solubility in water, low hygroscopicity, excellent carrier capabilities, non-toxicity, edibility, and limited solubility in anhydrous alcohol. In 2008, Cilurzo et al. introduced a film formulation using MDX as the sole material for film formation. Films made of MDXs had a drawback concerning their physical stability, as they tend to harden over time. The addition of a homopolymer or copolymer of vinyl acetate avoided hardening of the films based on MDX and plasticizer.

b. Pullulan: Pullulan is an exopolysaccharide that is primarily synthesized by yeasts, specifically the fungus Aureobasidium pullulans, as well as other microorganisms including Cytaria darwinii, Cytaria harioti, Teloschistes flavicans, Tremella mesenterica, Rhodotorula bacarum, and Cryphonectria parasitica. Pullulan is a biopolymer characterized by being non-ionic, non-hygroscopic, non-toxic, non-mutagenic, and non-carcinogenic. It exhibits lower viscosity in solution compared to other biopolymers. Additionally, pullulan is biodegradable, edible, odourless, tasteless, and displays solubility in both hot and cold water, as well as in dilute alkali solutions. Pullulan is utilized in the production of ODFs primarily because of its favourable film-forming characteristics. However, due to its high cost, it is commonly combined with synthetic, semi-synthetic, and natural polymers to reduce expenses and enhance other properties. Existing literature demonstrates the blending of pullulan with various polymers such as HPMC, pectin, maltodextrin, polyvinylpyrrolidone (PVP), trehalose, and okra biopolymer to achieve desired ODF formulations.

c. Starch: Starch, a plentiful polysaccharide, comprises two macromolecules known as amylose and amylopectin. Amylose is a linear polymer consisting of α-1,4 anhydroglucose units, which form a colloidal dispersion when mixed with hot water and possess remarkable film-forming capabilities. On the other hand, amylopectin is a highly branched polymer composed of α-1, 4 anhydroglucose chains connected by α-1,6 glucosidic branching points, rendering it completely insoluble. Starch can be sourced from diverse botanical species, including corn, wheat, potato, cassava, and rice. The starch obtained from each of these sources possesses distinct compositions and varying properties. The native starch exhibits a semi-crystalline nature that can exhibit undesirable traits such as low solubility or inferior mechanical properties. To improve its characteristics and functionality, starch can undergo chemical, enzymatic, or physical modifications. These modified starches can form uniform and water-loving films, in addition to offering favourable mechanical properties, rapid disintegration, and strong mucoadhesiveness.

2. Plasticizers: In order to achieve flexible and non-brittle orally disintegrating films (ODFs), the addition of a plasticizer is often necessary Water also acts as a plasticizer due to the significant water content that remains in ODFs even after the drying process. The presence of plasticizers lowers the glass transition temperature of the film-forming polymers, thereby enhancing the flexibility and elasticity of the resulting films. However, it is important to note that high concentrations of plasticizers can compromise the moisture resistance of the films, leading to instability or stickiness.

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 4, Jul.-Aug. 2023, pp: 1716-1723 www.ijprajournal.com ISSN: 2456-4494

3. Taste masking agent: Many active pharmaceutical ingredients (APIs) are known to possess unpleasant tastes. In order to overcome this issue, taste-masking excipients are frequently employed. The choice of taste-masking method depends on the physical condition of the API, whether it is dissolved or dispersed, as well as its solubility in saliva. Basic taste-masking approaches involve incorporating flavours, sweeteners, and bitter-blockers, while more complex techniques include particle coating, encapsulation, or complexation with ion exchange resins. It is important to note that larger particles used in these processes may cause scraping sensations during the casting of oral dose forms, resulting in an undesirable gritty mouthful.

d) Others: Fillers, colours, opacifiers, cooling agents, lubricants or antitacking agents, preservatives, and stabilisers are additional excipients for orally disintegrating films (ODFs). Citric acid is one saliva-stimulating substance that has been shown to increase salivation and speed up disintegration. With the right polymers, mucoadhesion can be improved. Penetration enhancers and buffering agents may increase buccal bioavailability if oral mucosal absorption is needed. Drug breakdown can be avoided by using enzyme inhibitors.

It may be required to use solubility enhancers for particular ODF formulations. Surfactants can promote salivation in the oral cavity and disseminate the coating mass more evenly throughout the intermediate liner. It could be required to use stabilisers and thickening agents to stop particle sedimentation. Guar gum and xanthan gum are examples of natural gums that can improve viscosity and film-forming abilities.

Formulation of ODF's: Steps involved in manufacturing of ODF's are as follows:

1. Formulation Development
2. Solution Preparation
3. Coating or Casting
4. Drying
5. Cutting
6. *in-vitro* and *in-vivo* testing
7. Packaging
8. Quality Control

Manufacturing Process: Orodispersible films (ODFs) can be manufactured through various methods, including solvent casting, hot melt extrusion, semisolid casting method, rolling method, or electrospinning.

1. Solvent Casting: Solvent casting represents one of the earliest techniques employed for the formulation of Oral Disintegrating Films (ODFs). This method is classified as a non-aqueous approach and is utilized for the production of both heat-stable and heat-sensitive pharmaceutical drugs in a solid dosage form.

Preparation of Oral Disintegrating Films (ODFs) involves several steps:

Firstly, a film-forming polymer is dissolved in either water, an organic solvent, or a mixture of solvents to create a suspension or emulsion. The use of an organic solvent offers two advantages: it enhances the solubility of the drug and reduces the production time of ODFs. Other excipients are then added to the solution obtained in the previous step. In the final step of solution preparation, the Active Pharmaceutical Ingredient (API) is added to the resulting viscous solution.

If the material to be casted is a suspension or emulsion, it is crucial to ensure homogeneity throughout the entire casting process. De-aeration of the casting solution is achieved through continuous stirring. The coating mass is then cast as a wide film onto a single belt or a release-coated substrate known as an intermediate liner. The desired drug content of the final strip is determined by the adjusted wet film thickness. The jumbo roll is subsequently cut into smaller patches of varying width, which are then further cut into the desired size. After cutting, the obtained patches are individually packed in aluminium pouches. The packing materials serve as a barrier against moisture.

2. Hot Melt Extrusion: The pharmaceutical industry needed a different approach, and hot-melt extrusion was discovered to provide a number of benefits. First off, there are no solvents required for processing oral films. Additionally, this technology may produce extrudes in a single step, which reduces processing costs by eliminating the need to compress medications and excipients. A homogeneous distribution of particles is made possible by melting active ingredients and polymers into a liquid state, followed by mixing, which increases a drug's bioavailability.

The hot-melt extruded technique is a versatile and efficient method for producing films with controlled drug release profiles. It involves combining the medication, film former, plasticizer, surfactants, and other necessary excipients. The formulation is then loaded into a hopper, allowing controlled feeding into the extruder. The components are carefully melted, and a screw mechanism transports the

International Journal of Pharmaceutical research and Applications
Volume 8, Issue 4, Jul.-Aug. 2023, pp: 1716-1723 www.ijprajournal.com ISSN: 2456-4494

molten material towards the extrusion die. To enhance adhesion to mucosal surfaces, additional measures can be taken during processing. The hot-melt extrusion technique offers a versatile and efficient method for producing films with uniform drug distribution, optimal thickness, and effective adhesion to target mucosal surfaces, advancing pharmaceutical research and development.

3. Semi-Solid Casting: The creation of orally disintegrating films (ODFs) also utilizes the semi-solid casting technique. This method involves several steps starting with the preparation of film-forming polymers and water-soluble solutions. These components are carefully combined and then added to an acid-insoluble polymer solution. The acid-insoluble polymer solution plays a crucial role in maintaining the structural integrity and stability of the ODFs.

The creation of ODFs also employs the semi-solid casting technique. This approach involves preparing film-forming polymers and water-soluble solutions, which are then added to an acid-insoluble polymer solution. In order to achieve the necessary gel mass, plasticizers are included into the previously produced solution in the appropriate ratios. The produced gel mass is cast under controlled circumstances as films with a thickness of 0.015 to 0.05 inches.

4. Freeze Drying: Freeze-drying is a good option for creating orodispersible films because it allows the active ingredients to be preserved while retaining their stability and bioavailability. The following steps are usually included in the process: To make a thin film, a liquid formulation including the active ingredient(s), film-forming agents, solvents, and other excipients is distributed over a flat surface or mold. After that, the film is frozen at low temperatures to solidify the formulation and prepare it for the next stage. When the frozen film is exposed to reduced pressure, the ice inside it sublimates, converting from a solid to a vapor without going through a liquid phase. This eliminates the film's solvent and water content. As the ice melts, it leaves a porous structure in the film. When the film comes into touch with saliva or water, its porous nature allows it to dissolve or disintegrate quickly. Depending on the intended usage, the orodispersible films are normally packed in individual dosage units or bulk containers once the freeze-drying process is completed.

Physical properties of ODF's: These characteristics are critical to the film's performance, simplicity of use, and overall user experience. Here are some critical physical features to consider:

1. Thickness: The thickness of the film is an important factor in determining how soon it dissolves or disintegrates in the mouth. Thinner films disintegrate faster in general. The comfort of handling and packing can also be affected by thickness. Thickness measurements are commonly made with tools like as micrometers or thickness gauges.

2. Weight: The weight of the film is determined by its composition and the amount of active ingredient(s) present. Accurate weight measurements aid in ensuring consistent dosing and medicine distribution. Analytical balances can be used to measure weight.

3. Flexibility: Flexibility refers to the film's ability to bend and conform without breaking. Flexible films are more comfortable to handle and are less likely to tear during application. Flexibility is often assessed qualitatively by manually as tensile strength and elongation measurements.

4. Tensile Strength**:** Tensile strength measures the maximum force a film can withstand before breaking when subjected to stretching or pulling. Higher tensile strength indicates better mechanical integrity and resistance to tearing during handling. Tensile strength is determined through mechanical testing equipment.

5. Elongation: Elongation measures the ability of a film to stretch before breaking. A higher elongation indicates greater flexibility. This property is often evaluated alongside tensile strength to assess the overall mechanical behavior of the film.

6 Texture and Surface Appearance: The texture and surface appearance of the film can impact the user's perception and acceptance of the product. Smooth and uniform surfaces are generally preferred, as they provide a pleasant mouthfeel and appearance.

7. Film Opacity: Opacity can affect the appearance of the film and how well the film adheres to the tongue. Opaque orodispersible films may appear less transparent, while transparent films can provide a more natural visual appearance.

These physical properties can be evaluated using a combination of techniques, including visual inspection, mechanical testing, and dissolution testing. Manufacturers and researchers often use these evaluations to optimize formulations and manufacturing processes to achieve desired performance and user acceptability for orodispersible films.

Evaluation of ODF'S: A variety of techniques, including organoleptic, disintegration time, dissolving, surface pH visual inspection, moisture content, swelling index, mechanical characteristics,

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transparency, and contact angle, can be used to evaluate manufactured ODFs.

1. Disintegration testing: Disintegration testing is a crucial quality control measure for orodispersible films (ODFs) to ensure rapid dissolution and ease of administration. It measures the time it takes for the film to break down into small particles upon contact with saliva, simulating real-world usage scenarios. Disintegration testing is conducted using specialized apparatus, such as the disintegration tester or disintegration apparatus, at controlled temperatures, with time measurement recorded. Acceptance criteria are defined by regulatory authorities or product specifications, ensuring the film effectively dissolves or disintegrates within a specified time frame for rapid drug release. Multiple units of the film are tested simultaneously, with sufficient replicates to ensure statistical significance. Detailed documentation of the test procedure, including apparatus details, test conditions, sample preparation, and results, is maintained to maintain consistency and accuracy.

2. Content Uniformity:The drug content in orally disintegrating films (ODF) is commonly determined using standard drug assay methods. European Pharmacopeias specify content uniformity limits ranging between 85% and 115%. To validate the dose uniformity of a manufactured batch of ODF, the most appropriate test is the uniformity of dosage units, which involves analyzing 10 individual ODF samples with a single dose. High-performance liquid chromatography (HPLC) is typically employed to determine the drug content in the final ODF dosage form. The content uniformity can be calculated using a standard assay method described in pharmacopeia's. To perform this test, a 1 cm2 ODF sample is dissolved in 100 mL of buffer solution. Aliquots of 2 mL are taken and diluted with buffer solution up to 10 mL. The diluted sample is then analyzed using a UV-Vis spectrophotometer, with the absorbance set according to the active ingredient used. The absorbance value obtained helps in estimating the amount of drug in the film and assessing drug content uniformity.

3. Disintegration testing is a crucial quality control measure for orodispersible films (ODFs) to ensure rapid dissolution and ease of administration. It measures the time it takes for the film to break down into small particles upon contact with saliva, simulating real-world usage scenarios. Disintegration testing is conducted using specialized apparatus, such as the disintegration tester or disintegration apparatus, at controlled temperatures, with time measurement recorded. Acceptance criteria are defined by regulatory authorities or product specifications, ensuring the film effectively dissolves or disintegrates within a specified time frame for rapid drug release. Multiple units of the film are tested simultaneously, with sufficient replicates to ensure statistical significance. Detailed documentation of the test procedure, including apparatus details, test conditions, sample preparation, and results, is maintained to maintain consistency and accuracy.

4. Moisture Content: Moisture content (MC) loss plays a significant role in assessing the hygroscopicity of a film. In a particular study, the evaluation of MC loss was conducted by weighing four films initially. These films were then placed in either a desiccator or a hot air oven set at 50°C. The films were subjected to these conditions until a constant weight of the films was achieved, indicating that the moisture content had reached equilibrium and no further weight loss occurred. This process allowed for the determination of the moisture content loss and provided insights into the hygroscopic behaviour of the films.

5. in vitro-Dissolution: In the context of in vitro dissolution testing for films, two official apparatuses, namely the paddle and basket apparatuses, have been commonly used. Sink conditions, where the concentration of the drug in the dissolution medium remains low throughout the testing, must be maintained. However, there are instances where the film floats on the dissolution medium, posing difficulties during testing. This problem is more prevalent with the paddle apparatus, which is why the basket apparatus method is often preferred.In a particular study, various media were employed in both apparatuses, including phosphate-buffered solution with a pH of 6.8, 0.1 N hydrochloric acid (HCl), purified water, gastric fluids, and intestinal fluids. During the testing, six aliquots of 5 mL were drawn from the dissolution medium after every minute, and additional samples were taken at specific time points, such as 8, 10, 12, 16, 20, and 30 minutes. The drawn samples were then analyzed using a UV spectrophotometer to measure the drug concentration and assess the dissolution behavior of the films.

6. Taste and Flavour: Analyzing the taste and flavor of orodispersible films (ODFs) is essential for ensuring patient acceptability and compliance,

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especially when dealing with pharmaceutical items. The taste and flavor of ODFs are important factors in establishing the entire user experience and can influence patient adherence to treatment regimens.

Here's how taste and flavor evaluation for orodispersible films is typically conducted:
a. Sensory Evaluation by Trained Panelists.
b. Sensory Evaluation by Consumer Panels.
c. Instrumental Analysis.
d. pH and Chemical Analysis.

Evaluation of taste and flavor is crucial for ensuring patient satisfaction and adherence to orodispersible films. It assists manufacturers in identifying ways to increase product palatability and generate a more favorable customer experience.

7. Stability and Shelf-life: The stability and shelf-life of orodispersible films (ODFs) pose vital concerns in order to ensure that the product maintains its quality, efficacy, and safety for the period of the desired storage term. The physical, chemical, and microbiological properties of ODFs must be evaluated throughout time under varied storage settings. Here's an overview of how stability studies and shelf-life determination for ODFs are carried out:
a. Stability Study Design.
b. Parameters Monitored.
c. Storage Conditions
d. Sampling and Testing.
e. Data Analysis.
f. Packaging Considerations.
g. Regulatory Considerations.

Strategies used to enhance palatability and patient acceptance: It is essential to improve the palatability and patient acceptance of pharmaceuticals, especially orodispersible films (ODFs), in order to improve medication adherence and overall patient experience. Several strategies can be used to improve the palatability and patient acceptance of ODFs:

1. Flavor Masking and Enhancement**:**
Sweeteners, natural flavors, and artificial flavors can be used to disguise or enhance the taste of active substances and excipients.
Bitter taste inhibitors can be used to diminish or eliminate bitter taste perception.

2.. Texture and Mouthfeel**:**
For smooth texture, Optimize the formulation to ensure a smooth and pleasant texture during dissolution, without gritty or chalky sensations. Mouth-coating: Formulations that create a thin, pleasant mouth-coating upon contact with saliva can improve the overall experience.
3. Sweeteners and Excipients**:** Sweetening agents: Select sweeteners that have a nice flavor and no unpleasant aftertastes. Excipients: Select and modify excipients carefully to improve overall sensory experience without compromising drug stability or performance.

4. Customized Flavors: Patient preferences: Tailor flavors to specific patient preferences, taking cultural and regional tastes into consideration.5. Visual Appeal: Color and appearance: Optimize the color and appearance of ODFs to make them visually appealing, which can positively influence patient acceptance.

6. Convenience and Packaging: Packaging design: Create user-friendly and easy-to-open packaging that enhances the patient's experience. Portability: Consider packaging formats that are convenient for on-the-go use.

7. Patient-Centric Design: Patient involvement: Engage patients in the development process to gather feedback and insights on taste preferences and sensory attributes.

8. Sensory Evaluation: Trained panels: Conduct sensory evaluations involving trained panelists to identify taste and flavor attributes that need improvement. Consumer panels: Gather feedback from actual consumers to assess their perceptions and preferences.

9. Patient Education and Counseling: Instructions: Provide clear instructions on how to take the medication, including guidance on proper administration of ODFs. Counseling: Healthcare professionals can educate patients about the unique benefits and ease of administration of ODFs.

10. Companion Products: Flavor enhancers: Provide optional flavor enhancers or mouth rinses that can be used before or after taking ODFs to improve the taste experience. Oral care products: Recommend oral care products, such as sugar-free gum or mints, to mitigate any after taste.

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II. Conclusion:

Over the past several decades, ODFs' shortcomings in terms of administration, bioavailability, solubility, and taste have made them a popular drug delivery technology. To increase compliance, an innovative medication delivery technique using oral thin films comprised of natural, synthetic, and semi-synthetic polymers has been developed. It is possible to create films using a variety of methods for oral routes as well as ophthalmic, rectal, vaginal, and transdermal drug delivery. Novel films can be utilised as alternatives to standard dosage forms and are able to easily get around their drawbacks. These problems have been resolved by formulation optimisation, and the future of film technology for drug delivery by any route is bright. This will help to resolve the problems associated with current methods.

Conflicts of Interest: The author declares no conflict of interest.

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