STM JOURNALS

Trends in
Drug Delivery

ISSN: 2394-7268
Volume 11, Issue 3, 2024
September–December
DOI (Journal): 10.37591/TDD

https://journals.stmjournals.com/tdd

Review TDD

A Review on Oral Thin Films: A New Approach to Effective and Easy Drug Delivery

P.N. Vaishnavi[1], Vedant Patel[1], Himanshu Solanki[1,*]

Abstract

Oral Thin Film (OTF) is an advanced drug delivery system in which a drug is incorporated into a dissolvable strip and placed in the oral cavity for rapid absorption. OTF is useful for patients, such as pediatric and geriatric, who have difficulty swallowing pills. It provides rapid action, precise dosage, and improved bioavailability. OTFs consist of fast-dissolving films, extended-release films, and mucoadhesive films for various therapeutic applications. The manufacturing processes of OTFs, such as solvent casting, hot melt extrusion, and semi-solid casting are specific to a particular formulation of the drug. OTFs can be used in many areas, such as pain relief, antiemetics, allergy treatment, nutritional products, and many others. However, despite these advantages, problems, such as moisture sensitivity, low drug loading capacity, and stability issues remain that need to be addressed for wider application. Recent advances in nanotechnology and personalized medicine promise to broaden the scope and effectiveness of OTFs in the future.

Keywords: Mouth dissolving film, solvent casting, hot melt extrusion, advantages, challenges of OTF

INTRODUCTION

Mouth dissolving films (MDFs) are a novel drug delivery system designed to dissolve quickly when placed on the tongue, offering a convenient and effective way to administer medications without the need for water. These thin, flexible strips are typically composed of water-soluble polymers, allowing them to disintegrate within seconds, releasing the active drug directly into the oral cavity for rapid absorption. Oral Thin Film (OTF) is a technology that delivers medication from a thin, flexible strip that dissolves in the oral cavity when exposed to saliva and will allow for fast drug absorption. OTFs are designed to make administration easier while increasing bioavailability and patient compliance, mainly in patients who have difficulty swallowing tablets or capsules, such as the elderly, pediatric, or psychiatric patients [1].

MDFs are gaining popularity due to their ease of use, especially among populations that may struggle with traditional dosage forms, such as children, the elderly, and those with swallowing difficulties (dysphagia). The films bypass the gastrointestinal tract and first-pass metabolism, which can enhance the bioavailability of certain drugs, providing faster onset of action.

***Author for Correspondence**
Himanshu Solanki
E-mail: drhimanshusolanki7ssrcp@gmail.com

[1]Associate Professor, Department of Pharmaceutics, SSR College of Pharmacy, Sayli, Silvassa, Union Territory of Dadra Nagar Haveli and Daman Diu, India

Received Date: October 03, 2024
Accepted Date: October 15, 2024
Published Date: October 28, 2024

Citation: P.N. Vaishnavi, Vedant Patel, Himanshu Solanki. A Review on Oral Thin Films: A New Approach to Effective and Easy Drug Delivery. Trends in Drug Delivery: 2024; 11(3): 22–41p.

MDFs are used for a variety of therapeutic applications, including pain management, allergy relief, and treatments for conditions, such as nausea, migraines, and cardiovascular diseases. The films offer several advantages over traditional tablets and capsules, such as eliminating the need for water, providing accurate dosing, and reducing the risk of choking [2].

Despite these benefits, challenges remain in the formulation of MDFs, particularly in achieving a balance between rapid disintegration, adequate

mechanical strength, and sufficient drug load. Nonetheless, continued research and technological advancements are expanding the potential of MDFs in drug delivery, making them a promising option for patients and healthcare providers alike [3].

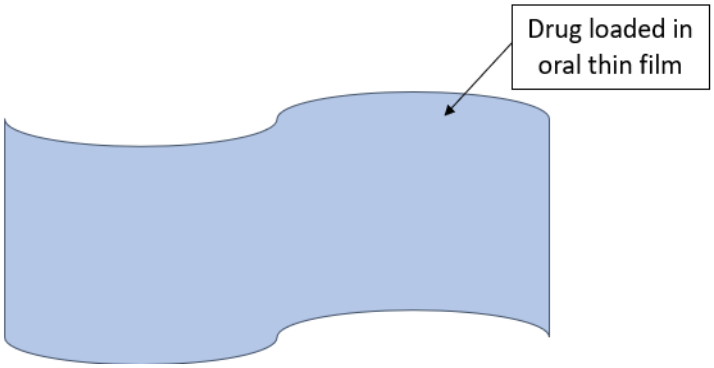

Figure 1. Image showing a drug-loaded oral thin film.

OTFs are typically formulated using hydrophilic polymers that rapidly disintegrate upon contact with saliva (Figure 1). The API is released either for local effect in the mouth or for systemic absorption through the oral mucosa, including sublingual or buccal routes [2]. The key advantages of OTFs include [4]:

1. *Fast dissolution:* The film should rapidly dissolve or disintegrate into the mouth, typically within seconds to a minute, without the need for water or chewing. This allows for quick drug release and absorption.
2. *Thin and flexible:* The film should be thin and flexible to ensure comfort during administration. It should easily adhere to the mucosal surface in the oral cavity without causing irritation.
3. *Taste masking:* Since many drugs have a bitter or unpleasant taste, the film should include taste-masking agents or flavors to improve the overall patient experience.
4. *Uniform drug distribution:* The active pharmaceutical ingredient (API) must be evenly distributed throughout the film to ensure consistent dosing and therapeutic efficacy.
5. *Mechanical strength:* While the film must be thin and flexible, it should also possess sufficient mechanical strength to handle packaging, storage, and transport without tearing or breaking.
6. *Rapid onset of action:* The film should allow the drug to be absorbed through the oral mucosa, leading to a faster onset of action compared to oral tablets, as it bypasses first-pass metabolism in the liver.
7. *Stability:* The film should be stable under various environmental conditions, such as temperature and humidity, without losing its efficacy or physical integrity.
8. *Non-sticky:* The film should not leave any residue or a sticky sensation in the mouth after dissolution, ensuring comfort and ease of use for the patient.
9. *Accurate dosing:* It should allow for precise control over the dosage of medication, which is critical for ensuring safety and efficacy, particularly for potent drugs or pediatric applications.
10. *Biocompatibility:* The excipients used in the film should be biocompatible and safe for oral use, avoiding any potential irritation or allergic reactions.

Historical Background and Development

OTF Film technology emerged in response to the need for alternative drug delivery systems that could ultimately overcome the limitations of traditional tablets and capsules. The history of OTFs dates to the early 1970s when drug delivery through the buccal and sublingual regions experimented in an attempt to reach the bloodstream much faster for drug action. These preliminary formulations provided the precursors for thin films, which were first used in breath fresheners and nicotine replacement therapies [5].

Key Historical Events Include

1. *1970s:* First studies on oral and sublingual drug delivery systems. The objectives were to avoid the gut and the first-pass metabolism which apparently provided faster therapeutic effects [6].
2. *1990s:* The technology becomes commercially viable as over-the-counter breath freshening strips, for Listerine® pocket packs, are introduced on to the market [7].
3. *Early 2000s:* Thin films were started to be used for pharmaceutical purposes including the introduction of nicotine replacement therapy films and for medications related to nausea and vomiting among many others [8].
4. *Since mid-2000s:* Thin films' use has gained immense ground among pharmaceutical firms for controlled release, higher stability, and combinations. Prescription drugs approved by FDA in thin film formulation include Zuplenz® for nausea [9].

TYPE OF OTFS

OTFs are formulated in varieties, so the selected formulation will release the API based on the desired therapeutic effect, release profile, and site of action in the oral cavity. The dominant categories of OTFs are Fast Dissolving Oral Films (FDOF), Extended-Release Films, and Mucoadhesive Films (Figure 2) [10].

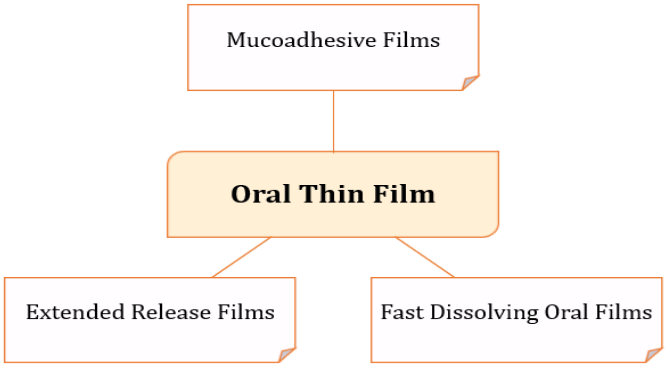

Figure 2. Types of oral thin films.

Fast Dissolving Oral Films (FDOF)

The FDOF are compounded to dissolve quickly in the presence of saliva. The oral films readily dissolve within seconds up to one minute, and depending upon the formulation, the active ingredient is absorbed through the oral mucosa or gastrointestinal tract. FDOFs possess excellent utility in conditions where immediate action of the drug is desirable, like in pain relief, antiallergics, and antiemetics [11].

Key Features [12]

- *Rapidly dissolves:* Dissolves quickly in the mouth without requiring water.
- *High oral bioavailability:* Avoids first-pass metabolism when absorbed through the oral mucosa.
- *Patient-friendly:* Pediatric, geriatric, and patients with dysphagia can take it easily.
- *Usage:* Commonly used anti-emetics, painkillers, antihistamines, and sedatives.

Example: Zuplenz® (Ondansetron): An FDOF for nausea that dissolves in under 30 seconds to provide immediate relief of chemotherapy-induced nausea.

Extended-Release Oral Films (EROF)

Extended-Release Oral Films are made to provide a prolonged release of the medication over an extended period.

Unlike fast-dissolving films, which dissolve fast, these films cause gradual drug release with a steady level of drugs in the bloodstream. This is made possible by employing special materials-for example, polymers-that control how the drug is released [13].

Key Features [14]

- The drug is released over for several hours therefore, sustained action, for prolonged effects.
- Reduce dosing frequency: This is important in chronic conditions, as sustained levels of the drug are required, avoiding increased frequency of dosing.
- Improve Patient Compliance.

Usage

Available to treat chronic pain, hormone replacement therapy, or another steady dose of an incorporated drug.

Challenges

To design an extended-release film, it is important to carefully choose polymers able to deliver the drug over time with the suitable rate of action and stability of the drug molecule. The novel must also remain structurally upright, administering the drug in high doses regularly.

Mucoadhesive Films

Mucoadhesive Oral Films are designed to adhere to the mucosal tissues within the mouth (buccal or sublingual areas). These films can remain in one place for a long time, resulting in either localized or systemic action. These are beneficial for drugs that should be in contact with the mucosa for an extended time to maximize absorption or require local delivery to treat oral cavity and throat disorders [15].

Key Features [16]

- *Locally or systemic activity:* Depending on the active ingredient, mucoadhesive films can deliver localized effects (treatment of oral ulcers) and buccal/sublingual systemic absorption.
- Primary adhesive properties allow the drug to be released over an extended contact time with the mucosal tissue.
- *Targeted delivery:* Useful for treating localized conditions in the mouth or throat, such as infections or pain, or for systemic absorption of specific drugs.
- *Applications:* Local treatment of oral diseases, hormone replacement therapies, and chronic pain.
- *Challenges:* Maintaining adhesion in a dynamic environment like the mouth, where saliva and movement are constant, requires precise formulation of adhesive polymers and careful drug release design (Table 1).

Table 1. Key features and application of different types of oral thin film.

Type	Key Features	Applications
Fast-Dissolving Films	Rapid dissolution, high bioavailability, immediate effect.	Anti-allergies, pain relief, nausea.
Extended-Release Films	Prolonged release, reduced dosing frequency.	Chronic pain, hormone therapy, psychiatric treatments.
Mucoadhesive Films	Prolonged contact, localized/systemic effect.	Oral ulcers, localized infections, hormone replacement.

MANUFACTURING TECHNIQUES FOR ORAL THIN FILMS

OTF manufacturing involves many processes, such as Solvent Casting, Hot-Melt exclusion, Semisolid casting, rolling etc. It is designed to ensure that the product is uniform, thin, and able to deliver the active ingredients appropriately (Figure 3) [17].

SOLVENT CASTING METHOD [18]

The solvent casting method is one of the most widely used techniques for manufacturing thin films, particularly in pharmaceutical applications, including the production of MDFs and other drug delivery systems. This method involves dissolving both the API and the excipients (such as polymers,

plasticizers, and other additives) in a solvent to form a homogenous mixture, which is then cast onto a substrate to form a thin film. Once the solvent evaporates, a uniform, solid film remains, containing the drug evenly distributed throughout (Figure 4).

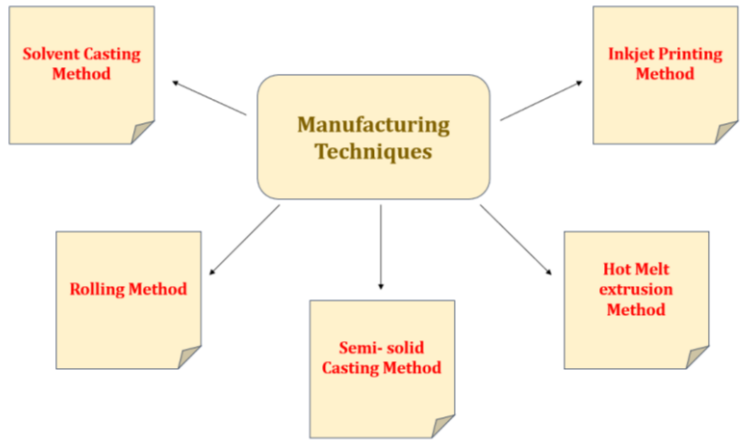

Figure 3. Methods of manufacturing OTF.

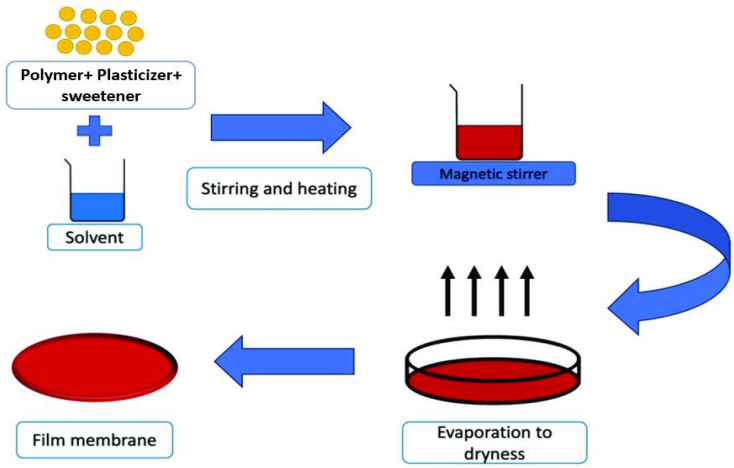

Figure 4. Schematic representation of solvent casting method.

Steps in the Solvent Casting Method

Selection of Ingredients

- *Polymers:* These form the backbone of the film. Commonly used polymers include HPMC, polyvinyl alcohol (PVA), and pullulan. The choice of polymer depends on the desired film properties, such as dissolution rate, mechanical strength, and compatibility with the drug.
- *API:* The drug is selected based on the therapeutic purpose. It must be soluble or dispersible in the solvent to ensure uniform distribution within the film.
- *Plasticizers:* These additives, such as glycerin or polyethylene glycol (PEG), provide flexibility and enhance the mechanical properties of the film.
- *Other excipients:* Sweeteners, flavoring agents, and colorants may be added to improve patient acceptance, particularly for orally dissolving films.

Preparation of Solution

- The polymer and other excipients are dissolved in a suitable solvent (e.g., water, ethanol, or organic solvents). The choice of solvent depends on the solubility of the ingredients and the required evaporation rate.

- The API is then dissolved or dispersed in this polymer solution. Careful mixing ensures the uniform distribution of the drug throughout the solution.

Casting the Solution

- The prepared solution is cast onto a flat surface or substrate, such as a glass or Teflon plate. The thickness of the film is controlled by adjusting the volume of the solution and the area of the substrate or using a doctor's blade to spread the solution uniformly.

Solvent Evaporation

- The cast solution is then dried, typically under controlled temperature and humidity conditions, to evaporate the solvent. As the solvent evaporates, the polymer solidifies, forming a thin, flexible film. The drying conditions must be optimized to ensure uniform drying and to prevent defects like cracks or bubbles.

Film Removal

- Once fully dried, the film is peeled off from the substrate. It should be uniform in thickness, free of defects, and have the desired mechanical properties. The film is then cut into the required shapes and sizes.

Packaging

- The final films are packaged in suitable materials to protect them from environmental factors like moisture and light, which could affect their stability.

Advantages of the Solvent Casting Method

- *Uniform drug distribution:* Since the drug is mixed into a homogenous solution before casting, it allows for even distribution of the API throughout the film, ensuring consistent dosing in each portion of the film.
- *Good control over film properties:* By adjusting the polymer concentration, plasticizers, and solvent evaporation conditions, the thickness, mechanical strength, and dissolution profile of the film can be controlled.
- *Versatility:* This method can be used to incorporate a wide range of drugs, including poorly water-soluble drugs, by selecting the appropriate solvent system and polymers.
- *Scalability:* The solvent casting method is suitable for both laboratory-scale preparation and large-scale production, making it flexible for different stages of drug development and commercialization.

Limitations of the Solvent Casting Method

- *Residual solvent:* The presence of residual solvent in the final film can be a concern, especially if organic solvents are used. Proper drying techniques are necessary to minimize solvent residues, as these can affect the film's safety and stability.
- *Solvent selection:* The choice of solvent is critical, and the use of organic solvents may pose toxic risks or environmental concerns. Additionally, some drugs may not be soluble in the available solvents.
- *Film defects:* Issues like air bubbles, cracking, or uneven film thickness can arise if the casting and drying process is not carefully controlled.

Applications of the Solvent Casting Method

- *Oral films:* Most used for making mouth-dissolving films (MDFs) and Buccal films, where quick drug release is essential for fast therapeutic action.
- *Transdermal patches:* The method is also used for producing transdermal drug delivery films, where the film adheres to the skin and delivers the drug systemically.
- *Edible films:* In the food industry, the solvent casting method is used to create edible films that can carry flavors, nutrients, or preservatives.

Hot Melt Extrusion Method [19]

Hot melt extrusion (HME) is a widely used pharmaceutical manufacturing process for producing solid dosage forms, especially for formulating poorly soluble drugs. In this method, a drug and its excipients (polymers, plasticizers, etc.) are melted and mixed under high temperatures and pressure, then extruded through a die to form a uniform, solid product. The extruded material can be shaped into films, tablets, granules, or pellets. HME is particularly useful for enhancing drug solubility and bioavailability (Figure 5).

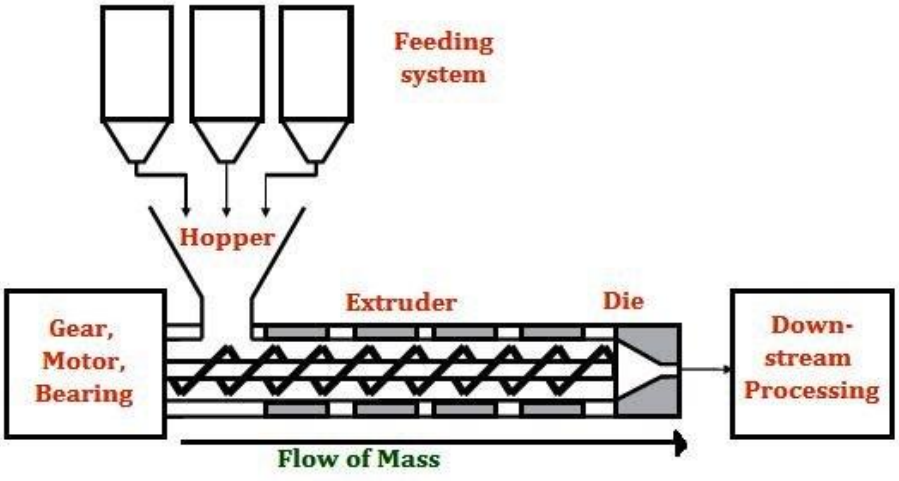

Figure 5. Schematic representation of hot melt extrusion method.

Steps Involved in HME

1. *Feeding:* The drug and excipients are first fed into an extruder. These materials are usually in powder form and may include polymers, binders, plasticizers, and other additives that facilitate the extrusion process or improve the product's properties.
2. *Melting and mixing:* Inside the extruder, the materials pass through heated zones where they are melted. The screws inside the extruder rotate and blend the ingredients uniformly, allowing the drug to be dispersed evenly in the polymer matrix. The temperature, speed, and screw design are carefully controlled to ensure proper mixing and prevent degradation of the drug.
3. *Extrusion:* The molten mixture is pushed through a die at the end of the extruder, which shapes the material into a desired form (e.g., a thin film, rod, or granules). The shape and size of the die depend on the intended final dosage form.
4. *Cooling and solidification:* After extrusion, the molten product is cooled, usually by passing through a cooling conveyor or air-cooling system. As it cools, the material solidifies into a stable form with a uniform composition.
5. *Downstream processing:* The solidified extrudate can undergo additional processing, such as cutting, milling, or forming into specific shapes like tablets or capsules. If making films, the extrudate can be rolled into thin sheets.

Advantages of HME

1. *Enhanced drug solubility:* HME can convert poorly soluble drugs into amorphous forms, improving their solubility and bioavailability. The drug is molecularly dispersed within the polymer matrix, leading to faster dissolution rates.
2. *No use of solvents:* Unlike other pharmaceutical processes, HME does not require the use of solvents, making it environmentally friendly and eliminating issues related to solvent removal and residual solvents.
3. *Continuous process:* HME is a continuous process, making it suitable for large-scale production. This reduces production time and is cost-effective compared to batch processes.

4. *Improved stability:* The polymer matrix in HME can protect sensitive drugs from degradation due to moisture, light, or oxygen. This enhances the shelf life and stability of the final dosage form.
5. *Versatility:* HME is used for producing a wide range of drug delivery systems, including immediate-release, sustained-release, and targeted delivery formulations. It is also useful for producing dosage forms like films, tablets, pellets, and implants.

Disadvantages of HME

1. *High processing temperatures:* The high temperatures used during HME can potentially degrade heat-sensitive drugs or excipients. However, this can be managed by selecting appropriate polymers with lower melting points or using plasticizers to lower the processing temperature.
2. *Limited API load:* In some cases, the drug loading capacity is limited due to the physical and chemical properties of the polymers used. High drug concentrations may affect the extrudability and mechanical properties of the final product.
3. *Specialized equipment:* HME requires specialized extruders and processing equipment, which can increase the initial setup costs for manufacturing.

Applications of HME

1. *MDFs:* HME is commonly used to produce thin, fast-dissolving films for drug delivery. These films dissolve rapidly in the mouth, offering quick onset of action.
2. *Sustained-release tablets:* HME can be used to produce tablets that release the drug slowly over time, offering a controlled-release profile.
3. *Solid dispersions:* HME is widely used to create solid dispersions of poorly soluble drugs to enhance their bioavailability.
4. *Transdermal patches:* The method is also used for producing films or patches that deliver drugs through the skin (transdermally).

Inkjet Printing [20]

Inkjet printing is an advanced and versatile technology used in various industries, including pharmaceuticals, for precise deposition of materials. In the context of drug delivery and pharmaceutical applications, inkjet printing is employed to print APIs and excipients onto substrates, creating dosage forms, such as oral films, tablets, or personalized medicines. The method provides high accuracy, precision, and flexibility in creating customized drug doses.

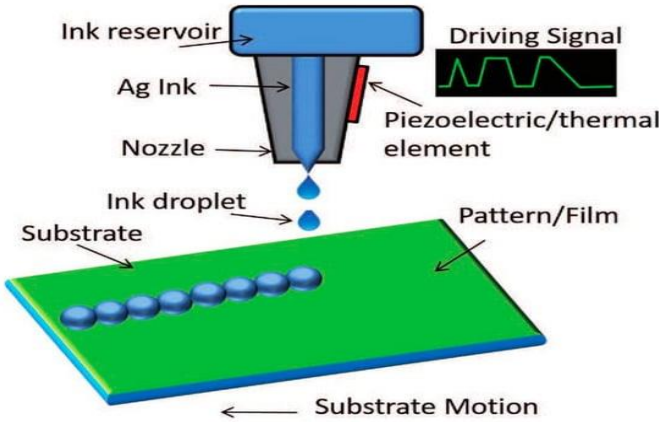

Figure 6. *Schematic representation of inkjet printing method.*

Working Principle of Inkjet Printing

Inkjet printing involves the controlled ejection of tiny droplets of ink or solution from a print head onto a substrate in a predefined pattern. In pharmaceutical applications, the ink or solution typically contains the API along with other excipients dissolved in a solvent (Figure 6). The basic mechanism of inkjet printing is based on two methods:

Thermal Inkjet Printing

- *Mechanism:* In this method, a heating element is used to rapidly heat a small volume of the ink solution in the print head. This creates a bubble, which expands and forces a droplet of the solution out of the nozzle onto the substrate.
- *Applications:* Commonly used for water-based inks or solutions with low viscosity, including APIs dissolved in water or alcohol-based solvents.

Piezoelectric Inkjet Printing

- *Mechanism:* Piezoelectric materials are used to generate pressure pulses. When an electric voltage is applied, the piezoelectric material contracts, pushing the ink droplet out of the nozzle.
- *Applications:* More suitable for a wide range of solutions, including those with higher viscosities.

This method is commonly used in pharmaceutical applications for precise drug printing.

Process of Inkjet Printing in Pharmaceuticals

- *Formulation of ink solution:* The drug API and excipients are dissolved or suspended in a suitable solvent to create an ink solution with appropriate viscosity and surface tension. This ink solution is loaded into the print head.
- *Droplet formation:* The inkjet printer generates droplets using either thermal or piezoelectric technology. The droplet size is carefully controlled, typically in the range of picoliters, to ensure precise dosing.
- *Droplet ejection and deposition:* The tiny droplets are ejected from the nozzle and deposited onto the substrate in a predefined pattern. The substrate can be oral films, tablets, or other dosage forms.
- *Drying and solidification:* Once the droplets are deposited, the solvent evaporates, leaving behind a thin layer of the drug on the substrate. This process may involve drying techniques like air drying or controlled heating.
- *Customization:* Inkjet printing allows for the customization of drug doses, shapes, and patterns on demand, making it ideal for personalized medicine. Multiple layers of drugs can be printed to achieve different release profiles or combination therapies.

Advantages of Inkjet Printing in Pharmaceuticals

- *Precision and accuracy:* Inkjet printing enables the precise deposition of micro-droplets, ensuring accurate dosing and uniform drug distribution across the substrate.
- *Customization and flexibility:* It allows for the creation of personalized medications tailored to individual patient needs, enabling precise control over drug dose, size, and shape. This is particularly beneficial for producing dosage forms for pediatric, geriatric, or special patient populations.
- *Minimal waste:* Compared to conventional drug manufacturing methods, inkjet printing uses minimal material, reducing waste during production.
- *Complex dosage forms:* The technology allows for the printing of complex dosage forms, including multilayer films, controlled-release profiles, and combination therapies, where different drugs are printed in separate layers.
- *Non-contact process:* Inkjet printing is a non-contact process, meaning the print head does not touch the substrate. This minimizes contamination risks and is ideal for fragile substrates or delicate drug formulations.
- *Scalability:* While inkjet printing is commonly used in small-scale production, it can be scaled up for larger pharmaceutical manufacturing, particularly for creating unique or personalized drug batches.

Limitations of Inkjet Printing in Pharmaceuticals

1. *Formulation challenges:* Not all APIs can be easily formulated into suitable ink solutions. The drug must be soluble or dispersible in the ink formulation, and the solvent used must not affect the stability of the drug.

2. *Nozzle clogging:* The tiny nozzles used in inkjet printing can be prone to clogging, especially when dealing with solutions that contain particulates or have high viscosity.
3. *Drying time:* The process may require careful control of the drying time and conditions to ensure the solvent evaporates without affecting the stability of the drug.
4. *Complex equipment:* The equipment for inkjet printing can be expensive and require precise calibration and maintenance to ensure optimal performance.

Applications for Pharmaceuticals

1. *Personalized medicine:* Inkjet printing allows for the creation of patient-specific doses, offering customized treatment options for individuals based on their medical needs.
2. *Oral films and tablets:* The technology is used to print APIs onto oral dissolving films (ODFs), creating thin, fast-dissolving dosage forms. It can also be used to print layers of drugs onto tablets, achieving controlled-release properties.
3. *Polypills and combination therapies:* Inkjet printing enables the layering of multiple drugs on a single substrate, allowing for combination therapies where different APIs are released at different rates or times.
4. *Research and development:* It is commonly used in R&D settings to create small batches of drugs for testing, without the need for large-scale production equipment.

Rolling Method [21]

The rolling method is a widely used technique for the manufacturing of ODFs. This method involves the formation of thin films by rolling a solution or suspension of drug and film-forming polymers on a surface, followed by drying and cutting into individual film units. It is a preferred method due to its simplicity, cost-effectiveness, and ability to produce uniform, flexible films with consistent drug distribution (Figure 7).

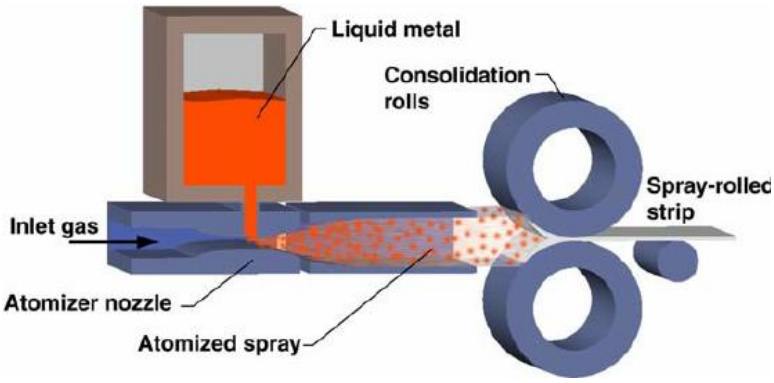

Figure 7. Schematic representation of rolling method.

Steps Involved in the Rolling Method

Preparation for the Film-Forming Solution/Suspension

- The process begins by preparing a homogeneous solution or suspension of the drug, film-forming polymers (like HPMC or pullulan), plasticizers (such as glycerin or PEG), and other excipients (e.g., sweeteners, flavoring agents, or stabilizers).
- The ingredients are dissolved in a suitable solvent, usually water or alcohol, to create a viscous mixture that can be spread easily.

Spreading the Solution/Suspension

- The prepared solution is then spread on a substrate using rollers. A specially designed rolling mechanism is used to control the thickness and uniformity of the film.
- The distance between the rollers determines the thickness of the film, which can be adjusted to achieve the desired thickness (usually between 50 and 150 microns).

Drying the Film

- After spreading, the film is passed through a drying chamber, where the solvent is evaporated, leaving behind a solid film.
- The drying temperature and time must be carefully controlled to ensure uniform drying without affecting the drug's stability.

Cutting the Film

- Once the film is dried, it is cut into individual strips or sheets of the desired size and shape.
- The cutting process must be precise to ensure that each piece contains the exact dosage of the API.

Packaging

- The cut films are then packaged in protective materials to prevent exposure to environmental factors, such as moisture, light, or oxygen, which could degrade the film or reduce its efficacy.

Advantages of the Rolling Method

- *Uniform drug distribution:* The rolling method ensures the drug is evenly distributed throughout the film, leading to accurate and consistent dosing.
- *Scalability:* It is easy to scale up large-scale production, making it a cost-effective method for industrial manufacturing.
- *Customization:* The film thickness, drug load, and excipient composition can be easily adjusted according to the therapeutic needs.

Applications

The rolling method is widely used for manufacturing MDFs, transdermal films, and other types of thin films for drug delivery. It is suitable for both immediate-release and controlled-release formulations.

Semi-Solid Casting Method [22]

The semi-solid casting method is a widely used technique for the manufacturing of oral films, particularly MDFs and other drug delivery films. This method involves creating a viscous or semi-solid solution of the drug, polymers, and other excipients, which is then cast into thin films. Once the film is formed, it is dried to obtain the final product. This process is favored for its ability to ensure uniform drug distribution and precise control over film thickness (Figure 8).

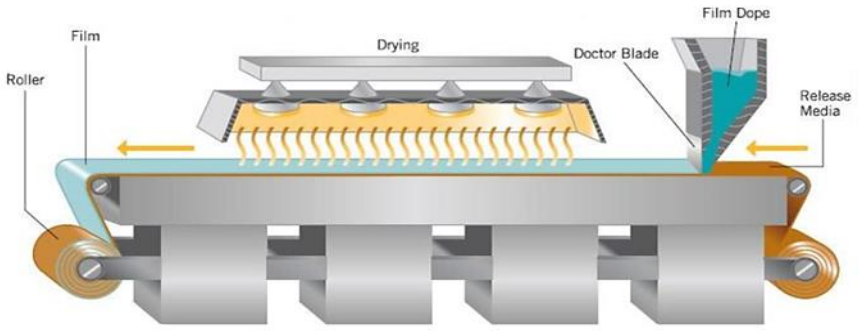

Figure 8. *Schematic representation of semi solid casting method.*

Steps Involved in the Semi-Solid Casting Method

Preparation of the Drug-Polymer Solution

- The first step involves dissolving or dispersing the drug and other excipients (such as plasticizers, sweeteners, flavoring agents, and taste-masking agents) in a suitable solvent, typically water or ethanol.

- Hydrophilic polymers like HPMC, pullulan, or PVA are commonly used to form the base of the film. These polymers are responsible for the film's structural integrity and dissolution properties.
- The mixture is stirred thoroughly to ensure homogeneity, ensuring that the drug is evenly distributed within the polymer matrix.

Formation of a Semi-Solid Solution

- The prepared solution has a viscous, semi-solid consistency due to the presence of the polymer, which allows it to form a uniform film when spread.
- The semi-solid nature of the solution is crucial for the next step, as it ensures that the solution can be cast evenly without running or separating.

Casting the Solution

- The semi-solid solution is then poured or spread onto a flat casting surface, such as a glass or metal plate. This can be done using various techniques like a casting knife or doctor blade, which ensures the solution is spread into a uniform layer.
- The thickness of the film can be precisely controlled by adjusting the gap between the casting knife and the plate. This is critical to ensuring consistent film thickness across the batch.

Drying the Film

- Once cast, the semi-solid solution is subjected to drying, usually in an oven or under controlled temperature and humidity conditions. The drying process removes the solvent from the film, leaving behind a solid, uniform film.
- The drying temperature and time must be optimized to avoid degradation of heat-sensitive drugs and to prevent the film from becoming brittle.

Cutting and Packaging

- After the film has dried, it is peeled off the casting surface and cut into individual strips or desired sizes, depending on the dosage form.
- The films are then packaged in moisture-resistant packaging to ensure stability and prevent degradation during storage.

Advantages of the Semi-Solid Casting Method

- *Uniform drug distribution:* This method allows for a homogeneous distribution of the drug within the film matrix, ensuring consistent dosing in each strip.
- *Controlled film thickness:* The thickness of the film can be easily controlled, which is important for determining the dosage and dissolution rate.
- *Scalability:* The semi-solid casting method is easily scalable, making it suitable for both small-scale lab production and large-scale industrial manufacturing.
- *Compatibility with various drugs:* The method can accommodate a wide range of APIs, including heat-sensitive drugs, as the drying temperatures can be adjusted accordingly.

Limitations of the Semi-Solid Casting Method

- *Solvent residue:* If organic solvents are used, careful drying is necessary to remove solvent residues, which could affect the film's safety and quality.
- *Limited drug loading:* Only a limited amount of drug can be incorporated into the film without affecting its mechanical properties, such as flexibility and strength.
- *Time-consuming:* The drying process can be time-consuming, and precise environmental control is often required to prevent defects like bubbles or cracks in the film.

MECHANISM OF ACTION OF ORAL THIN FILMS (OTFS)

Mechanism of Action of OTFs

OTFs are administered via the oral route to administer drugs in the patients' bodies. The mechanism of action is largely derived from the process of film dissolution that leads to drug absorption in the body. The major steps involved in the mechanism are as follows:

Dissolution in Oral Cavity [23]

- As soon as placed inside the oral cavity, either on the dorsum of the tongue, or buccally against the buccal mucosa, the OTF quickly begins to dissolve due to the saliva.
- The film-forming polymers are water-soluble, hydrophilic; therefore, the film disintegrates and dissolves in a few seconds to minutes depending on the formulation.

Factors Affecting Dissolution

- Type and concentration of polymer.
- Concentration of Plasticizers that enhance flexibility and improve dissolution
- Presence of surfactants that helps with the wettability of the film to aid in dissolution
- The thickness and size of film that dissolve faster when thin.

DRUG ABSORPTION THROUGH BUCCAL OR SUBLINGUAL MUCOSA [24]

Buccal and Sublingual Mucosa

- The inside of the cheek and underside of the tongue is mucosa, highly vascularized which enhance drug absorption and provides drugs immediately enter into systemic circulation, bypassing GI tract passage and hence avoid first-pass metabolism by the liver.
- For oral mucous surfaces, the thin epithelium layer favors the rapid diffusion of the drug into blood.

Absorption Process

As the film dissolves, the API comes in solution form and directly meets the mucous membranes. lipophilic drug or drug with high degree of membrane permeability are absorbed rapidly through the mucosal layers. Drug enters the bloodstream via passive diffusion or in some cases, through specialized transport mechanisms present in the oral mucosa.

Advantages of Buccal/Sublingual Absorption

- *Rapid onset of action:* The absorption of the drug via mucosal routes is quicker than through oral ingestion route and achieves the therapeutic effect very rapidly.
- *Bypass first-pass metabolism:* Since the drug bypasses the liver, it maintains higher bioavailability compared to drugs taken orally.
- *Improve patient compliance:* This method is non-invasive, convenient, and avoids the need for water or swallowing, which is especially beneficial for pediatric and geriatric patients.

ADVANTAGES OF ORAL THIN FILMS (OTFS) [25–27]

In comparison to the traditional oral dosage forms like tablets and capsules, there are several advantages of OTFs. Some of which include its acceptance among certain patient populations and drug delivery scenarios. These advantages are mentioned as follows:

Convenience and Compliance

- *Ease of use:* OTFs are easy to administer, especially in patients who may have a problem with swallowing pills, such as children, the elderly, or patients with dysphagia.
- *Improving patient compliance:* Due to their small, thin, and easy-dissolving nature, their compliance can be improved. Furthermore, OTFs are portable and easy to store.
- *Taste masking:* Sweetening agents, flavoring agents, as well as colorants may be added to enhance the odor and color in such a way that it is acceptable to patients.

Quick Onset of Action

- *Rapid drug release:* They dissolve quickly in the mouth to deliver the drug immediately after administration. This leads to fast absorption during sublingual or buccal administration routes.
- *Rapid therapeutic response:* Instant release and absorption through the richly vascularized oral mucosa gives a faster acting response than ordinary oral tablets or capsules.

No Need for Water

- *Convenient administration:* With OTFs, the active ingredient dissolves in the buccal cavity or on the tongue and can be administered without the aid of water. This makes them very useful for patients who are afflicted by difficulty swallowing or in cases where they have no access to clean water (e.g., during travel).
- *Usage on-the-go:* OTFs are appropriate for busy or mobility patients as they can be taken at any given time and place without preparation.

Ideal for Pediatric and Geriatric Patients

- *Pediatric suitability:* The child does not like to take tablets or capsules. So, OTF would be preferably acceptable with good taste and easy dissolution.
- *Geriatric suitability:* It is easy to administer and benefits geriatric patients more so those with dysphagia. The fact that it does not require the use of water, and its rapid onset of action is a benefit since these older people may have dexterity and cognitive failure.
- *Safe for special populations:* OTFs are a quite acceptable dosage form for psychiatric patients or neurologic patients in which the oral dosage form may not be tolerated.

Bypassing the First-Pass Effect

- *Avoids first-pass metabolism:* Drugs absorbed through the buccal or sublingual mucosa enters the systemic circulation directly, bypassing the liver and avoiding first-pass metabolism, which can significantly reduce the bioavailability of some drugs when taken orally.
- *High bioavailability:* OTFs increase the bioavailability of drugs subject to heavy metabolism in the liver, allowing lower doses to achieve the therapeutic effect.
- Reduced gastrointestinal side effects since OTFs are not absorbed by the gastrointestinal tract, this causes them to result in the minimization of irritation or common side effects caused by oral medication.

CHALLENGES AND LIMITATIONS OF ORAL THIN FILMS (OTFS)

Where OTFs possess advantageous characteristics, however, they also possess some challenges and shortcomings about their development and use. These aspects must be appropriately controlled during formulation and manufacturing [28–32]. Below are the key challenges:

Stability of Formulations

- *Chemical stability:* It should not lose its potency and efficacy throughout the shelf life of the product. The thin, exposed surface area of the film may catalyze the degradation of sensitive drugs, if not provided proper preservation.
- *Interaction with excipients:* Various excipients (such as film-forming polymers, plasticizers, and sweeteners) used in OTFs should not be incompatible with an API. Incompatibility leads to degradation or loss of activity with time.
- *Moisture sensitivity:* Some of the polymers in OTFs that are water-soluble or hygroscopic will absorb moisture, which can cause alterations in texture, film brittleness, or even degradation of the API.

Limited Drug Loading Capacity

- *Low dose drugs:* OTFs are highly suitable for low-dose drugs as very small amounts of APIs can be incorporated within the thin film matrix without affecting its mechanical properties or its dissolution rate.
- *Challenges with high-dose drugs:* For medications requiring larger doses, it can be difficult to achieve the necessary drug load within the film without making the film too thick, affecting its ability to dissolve quickly and uniformly in the oral cavity.
- *Constraints of API type:* OTFs are better suited for drugs that are potent and act at a very low dose. Those that require high doses may need alternative forms of delivery.

- Sensitivity to Environmental Factors
- *Moisture:* OTFs are typically very sensitive to moisture since the film-forming polymers may be hydrophilic. Premature dissolution, reduced stability, or even alteration in mechanical properties, like flexibility of films, could be the outcome of exposure to moisture.
- *Temperature sensitivity:* Store depending on the specific API and most of the excipients. Their storage conditions may be temperature sensitive, and hence, conditions that may be available for OTFs especially when they are in transport or shipped to areas with extreme climates.
- *Packaging requirements:* Because of their sensitivity to environmental variables, such as moisture and temperature OTFs must be packaged uniquely, for example, in moisture-barrier blister packs. Product stability then may be impaired and adds cost to production.

Taste Masking Issues

- *Bitter tasting drugs:* Because OTFs dissolve in mouth, the drug comes into direct contact with taste buds, making it difficult to mask the bitter or unpleasant taste of some APIs. Taste masking is essential for compliance pediatric or geriatric populations.
- *Complex taste masking techniques:* The use of additional equipment or coating techniques may be necessary to mask taste. This may complicate the production of the drug. In some cases, it might interfere with the release profile or efficacy of the drug altogether.
- *Flavor stability:* Flavors and sweeteners are added primarily for flavor enhancement; however, flavor acceptance by patients will decline with the passage of time because flavor constituents degrade.

APPLICATIONS OF ORAL THIN FILMS (OTFS)

OTFs are a promising multidrug delivery system, used widely in many therapeutic fields. Its properties position it well for pharmaceutical as well as for non-pharmaceutical applications. Some of the main areas of application include but are not restricted to are:

Therapeutic Uses

- *Pain management* [33]*:* OTFs can be combined with analgesic drugs like opioids and non-opioid analgesics for the rapid relief of both acute and chronic conditions of pain. The fast onset of action makes them very useful for the conditions mentioned above and therefore, are employed in various conditions. Example: Fentanyl OTFs is mainly prescribed for pain management in cancer patients.
- *Antiemetic* [34]*:* OTFs can be easily dispensed to patients with anti-nausea and anti-vomiting drugs if they cannot absorb oral tablets in the stomach due to vomiting.
  - *Example:* OTFs of ondansetron for prevention of nausea and vomiting related to chemotherapy, radiation, or surgery
- *Antiallergic* [35]*:* Preparations that consist of antihistamines like diphenhydramine or loratadine can be made as OTFs to remedy on-the-spot allergic reactions, such as hay fever or urticaria.
- *Other therapeutic areas:* Medicines meant to be used against anxiety, epilepsy, or insomnia are also formulated successfully as OTFs that could easily be used for fast action and ease of administration.

Nutraceuticals and Over the Counter (OTC) Drugs

- *Dietary supplements* [36]*:* OTFs are increasingly being accepted as vehicles for delivering vitamins, minerals, and other nutraceuticals in health and wellness applications. Their strength lies in an easy-to-consume daily supplement.
  - *Examples:* Vitamin B12, folic acid, and multivitamin supplements in OTF form.
- *OTC medications:* OTFs may be used to deliver over-the-counter drugs where most of the accepted products include cold and flu, allergy relief, or sleep aids.
  - *Examples:* Cough suppressants, decongestants, or melatonin OTFs for sleep disorders.

Pediatric and Geriatric Drug Delivery

- *Pediatric drug delivery* [37]*:* Children usually cannot swallow tablets or capsules; therefore, OTFs are a child-friendly substitute with an appealing flavor and easy delivery to ensure better compliance and accurate dosing.
  - *Applications:* Fever-reducing drugs (e.g., acetaminophen), antihistamines, or pediatric vitamins via OTF.
- *Geriatric drug delivery* [38]*:* Elderly patients are primarily susceptible to dysphagia or the difficulty of swallowing. OTFs can be administered in a form that does not require taking water and are designed for easy administration of chronic condition medicines.
  - *Applications:* Medications for cardiovascular diseases, anti-anxiety medications, or supplements used in cases of aging-related deficiency.

Veterinary Applications [39]

- *Animal medication:* This is hard to give to animals, especially because it comes as ordinary tablets or capsules. OTFs can be of practical use in the administration veterinary drugs: the film can be used to place on the tongue of the animal or mix with food.
  - *Applications:* Pain killers, anti-inflammatory drugs, or supplements, such as vitamins and minerals for animals and livestock.
- *Increased compliance:* The use of OTFs is easier in the administration of animals, ensuring better compliance than pills that animals may be resistant to.

REGULATORY AND QUALITY CONSIDERATIONS FOR ORAL THIN FILMS (OTFS)

Strict regulatory requirements must be adhered to in the development and commercialization of oral thin films or OTFs so that those products would be of quality, safe, and effective. More specific regulatory considerations include adherence to regulations stipulated by the FDA, EMA, and Good Manufacturing Practices (GMP).

IMPORTANT FACTORS TO CONSIDER REGULATIONS AND QUALITY

Guidelines from the FDA and EMA

- *FDA Guidelines (U.S. Food and Drug Administration):* The FDA considers OTFs to be oral transmucosal dosage forms, and they are subject to the same regulatory standards as other solid oral dosage forms, such as tablets and capsules.
- *New Drug Application (NDA) or Abbreviated NDA (ANDA):* Submission of a New Drug Application (NDA) or Abbreviated NDA (ANDA) is required for an orally disintegrating tablet (OTF) with a new drug or a generic of an approved drug. Manufacturers need to provide the FDA with information on the product's formulation, clinical data, and manufacturing processes.
- *The FDA Guidance for Industry:* Quality Considerations for Oral Drug Products, there are several quality monitor products that include dissolution testing, dose uniformity, and bioavailability studies.
- *EMA Guidelines (European Medicines Agency):* Like the FDA, the EMA applies the framework for the oral dosage form in regulating OTFs.The pharmacokinetic and pharmacodynamic properties should be demonstrated for OTFs by the Committee for Medicinal Products for Human Use. CHMP guidelines on bioequivalence and dissolution testing.
- *Market authorization applications (MAAs):* Like NDA with FDA, the EMA requires comprehensive dossiers known as MAAs for new or generic OTFs.

Good Manufacturing Practices (GMP)

- *GMP compliance:* OTFs shall be manufactured according to the principles of GMP which ensures consistency, quality, and safety at the time of manufacture.
- *Facilities and equipment:* All manufacturing facilities will include clean rooms with proper ventilation and controls for temperature and humidity to ensure that the OTFs remain stable and contaminant-free.

- *Process validation:* All stages of the manufacturing process, starting with raw material selection, through to the final packaging stage, must be validated ensuring all films meet a predetermined standard of quality.
- *Quality control:* This would include in-process controls, like weight and thickness uniformity, tensile strength, and finished product testing, like dissolution rate and drug content.
- *Hygroscopy and hygroscopicity:* OTFs are sensitive to environmental conditions, including humidity. Therefore, manufacturers take extra care during manufacturing and packaging to prevent moisture absorption.

Stability Testing and Shelf Life

- *Stability testing:* Stability testing is highly important, just to know the shelf life of the OTF, and to confirm that the drugs must remain potent, effective, and safe for the intended shelf life. According to the ICH Q1A (R2) guidelines, OTFs will be tested for any change in drug potency and physical integrity, such as those required by film disintegration under rigorous long-term, intermediate, and accelerated stability testing, besides being studied for any interactions between excipients and APIs.
- *Environmental factors:* OTFs often are sensitive to moisture, hence there is an assessment of how temperature, humidity, and light have been able to affect the stability of the product.
- *Shelf life:* The shelf-life is assigned based on stability studies. Manufacturers will observe over time such factors as moisture absorption, drug degradation, and physical integrity.
- *Packaging:* Proper use of packaging, that ensures extended shelf life by protecting the product from moisture, exposure to the environment, and other damaging factors. For example, aluminum foil or blister packs.

RECENT INNOVATIONS AND FUTURE TRENDS IN ORAL THIN FILMS (OTFS)

Advances in drug delivery technologies, nanotechnology, and personalized medicine have put OTFs on significant advances. These advances extend the horizon of OTFs, which contain more sophisticated drug formulations and higher bioavailability with tailor-made therapeutic effects. Among the recent innovations and trends are discussed below:

Nanotechnology in OTFs [40]

- *Nanoparticles for enhanced drug delivery:* Integrating nanotechnology into OTFs can greatly improve the solubility, stability, and bioavailability of drugs, particularly for those with low water solubility. Nanoparticles like nanocrystals, liposomes, or solid lipid nanoparticles can be incorporated into the film matrix to enhance drug absorption in the oral mucosa.
- *Targeted drug delivery:* Nanoparticles may also be engineered to deliver drugs more specifically to the targeted tissues, which can potentially enhance the therapeutic result with fewer side effects.
- *Increased drug load capacity:* Nanoparticles increase the ability of OTFs, so higher doses or even drugs that are very hard to formulate in thin films can be incorporated.
    - *Examples:* Nano-emulsions and nanosuspensions have been used in OTF formulations for the improvement of bioavailability of lipophilic drugs like cannabinoids, or poorly soluble APIs. Silver nanoparticles and other metal-based nanomaterials are being explored for their antimicrobial properties, useful in films for wound care or oral hygiene products.

Personalized Medicine via Oral Films [41]

- *Customized drug dosing:* The OTFs concept allows for personalization of the dosing of drugs to meet specific needs. This is particularly important in chronic diseases, pediatric, and geriatric populations, where one-size-fits-all standard dosing is not optimal for all patients.
- *On-demand printing of oral films:* the technological advances available in inkjet and 3D printing technologies result in the accurate deposition of APIs on OTFs, which can be used for customized drug dosing. It may be used for film preparation and provide drugs at specific doses, depending on a patient's genetic profile, disease progression, and/or his own metabolism.
- *Multiple APIs in a single film:* OTFs may be designed to release more than one active ingredient in one film. This will enable polypharmacy solutions in chronic diseases, where the patient must take multiple drugs every day.

Example

- Pharma Print and similar systems are currently being designed to allow healthcare providers to print for individual patients precisely the appropriate amounts of oral films with exact dosages and treatment regimens. Films can be designed with tailor-made dissolution profiles, which can accommodate immediate or controlled-release formulations as per the requirement by a specific patient need.

Smart Films with Controlled Release [42]

- *Controlled and sustained release systems:* The smart film known as the latest-generation OTFs is designed to deliver drugs in a controlled or sustained manner. These polymers change how they release based on different factors like pH, temperature, and oral cavity enzymes.
- *Multilayer films:* The films possess more than one layer or drug reservoir, which would allow the APIs to release at varied time intervals or under the influence of some external stimuli. In situations where continuous drug release is required, the product would be suitable for both immediate and prolonged drug delivery.
- *Bio-adhesive films:* These films adhere to the oral mucosa. The rate of release of the drug is gradual and constant over a period of days or weeks that is satisfactory for drugs requiring prolonged contact with the mucosal surface for absorption, such as in local treatments or drugs of poor bioavailability.

Examples:

- Temperature-sensitive polymers are used to film drugs which can be released at different rates under either bodily temperature or applied external heat.
- pH-sensitive films could be prepared based on local pH value to release drugs at specific areas of the mouth, such as the buccal or sublingual regions.
- Orally dissolvable films containing biodegradable nanocapsules that release drugs over time as the film dissolves gradually.

CONCLUSIONS

OTFs are one of the transformative approaches to drug delivery, as they provide patients with a more accessible alternative to conventional dosage forms like tablets and capsules. Their quick onset of action, user-friendliness in administration, and possible facilitation of an enhanced drug bioavailability offer important and useful tools in modern therapeutics. Their development, though, poses following challenges: stability of active drugs, masking the taste of the drug, and complexity of formulation. Further innovations, mainly in nanotechnology and personalized medicine, would likely overcome some of these limitations, thereby opening OTFs to a broad range of applications across different therapeutic areas. OTF research shall increasingly make it depend on OTF technology the ability to offer better patient outcomes and more personalized treatment options.

REFERENCES

1. Ozakar RS, Ozakar E. Current overview of oral thin films. Turk J Pharm Sci. 2021;18(1):111–121. doi: 10.4274/tjps.galenos.2020.76390.
2. Jain P, Gupta A, Darwhekar G. An detailed overview on mouth dissolving film. J Drug Delivery Ther. 2023;13(7):172–176.
3. Pingale PL, Shinkar DM, Boraste SS, Amrutkar SV. Formulation evaluation and characterization of mouth dissolving film of cisapride. Curr Trends Biotechnol Pharm. 2022;16(4):490–499. doi: 10.5530/ctbp.2022.4.82.
4. Joshua JM, Hari R, Jyothish FK, Surendran SA. Fast dissolving oral thin films: An effective dosage form for quick releases. Int J Pharm Sci Rev Res. 2016;38(1):282–289.
5. Khan N, Dogra SS, Saneja A. The dawning era of oral thin films for nutraceutical delivery: From laboratory to clinic. Biotechnol Adv. 2024:73:108362. doi: 10.1016/j.biotechadv.2024.108362.
6. Reddy PC, Chaitanya KS, Rao YM. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru. 2011;19(6):385–403.

7. Pham CL, Wood AJ, Lambert MB, Carpenter W. Palatal erythema in patients using listerine cool mint pocketpaks oral care strips. J Dent Child (Chic). 2005;72(2):52–55. doi:
8. Karki S, Kim H, Na SJ, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. Asian J Pharm Sci. 2016;11(5):559–574. doi: 10.1016/j.ajps.2016.05.004.
9. Park H, Otte A, Park K. Evolution of drug delivery systems: From 1950 to 2020 and beyond. J Control Release. 2022;342:53–65. doi: 10.1016/j.jconrel.2021.12.030.
10. Barnhart SD. Thin film oral dosage forms. In: Modified-release drug delivery technology. 2008. pp. 235–256). CRC Press.
11. Saxena A, Singh T. Oral dissolving films: a comprehensive review on recent perspectives and current approach to effective drug delivery. J Drug Delivery Ther. 2022;12(2):139–147. doi: 10.22270/jddt.v12i2.5244.
12. Maheshwari S, Singh A, Varshney AP, Sharma A. Advancing oral drug delivery: The science of fast dissolving tablets (FDTs). Intelligent Pharmacy. 2024. doi: 10.1016/j.ipha.2024.01.011,
13. Nashed N, Lam M, Nokhodchi A. A comprehensive overview of extended-release oral dosage forms manufactured through hot melt extrusion and its combination with 3D printing. Int J Pharm. 2021;596:120237. doi: 10.1016/j.ijpharm.2021.120237.
14. Adepu S, Ramakrishna S. Controlled drug delivery systems: Current status and future directions. Molecules. 2021;26(19):5905. doi:
15. Sharma R, Kumar S, Malviya R, Prajapati BG, Puri D, Limmatvapirat S, et al. Recent advances in biopolymer-based mucoadhesive drug delivery systems for oral application. J Drug Del Sci Tech. 2023;91:105227. doi: 10.1016/j.jddst.2023.105227.
16. Alaei S, Omidian H. Mucoadhesion and mechanical assessment of oral films. Eur J Pharm Sci. 2021;159:105727. doi: 10.1016/j.ejps.2021.105727.
17. Godbole A, Joshi R, Sontakke M. Oral thin film technology-current challenges and future scope. IJAREAS. 2018;7(2). doi:
18. Siemann U. Solvent cast technology–a versatile tool for thin film production. In: Scattering methods and the properties of polymer materials. Berlin, Heidelberg: Springer Berlin Heidelberg; 2005. pp. 1–14.
19. Pimparade MB, Vo A, Maurya AS, Bae J, Morott JT, Feng X, et al. Development and evaluation of an oral fast disintegrating anti-allergic film using hot-melt extrusion technology. Eur J Pharm Biopharm. 2017;119:81–90. doi: 10.1016/j.ejpb.2017.06.004.
20. Chou WH, Gamboa A, Morales JO. Inkjet printing of small molecules, biologics, and nanoparticles. Int J Pharm. 2021;600:120462. doi: 10.1016/j.ijpharm.2021.120462.
21. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. Int J Chemtech Res. 2010;2(1):576–583.
22. Singh P, Farooqui N, Bisht R, Manocha N. Formulation and evaluation of mouth dissolving film using semi solid casting method. International Journal of Pharmacy & Life Sciences. 2023;14.
23. Jacob S, Boddu SH, Bhandare R, Ahmad SS, Nair AB. Orodispersible films: current innovations and emerging trends. Pharmaceutics. 2023;15(12):2753. doi: 10.3390/pharmaceutics15122753.
24. Narang N, Sharma J. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci. 2011;3(Suppl 2):18–22.
25. He M, Zhu L, Yang N, Li H, Yang Q. Recent advances of oral film as platform for drug delivery. Int J Pharm. 2021;604:120759. doi: 10.1016/j.ijpharm.2021.120759.
26. Juluru NS. Fast dissolving oral films: A review. Int J Adv Pharm Biol Chem. 2013 Jan;2(1):108–112.
27. Ghodake PP, Karande KM, Osmani RA, Bhosale RR, Harkare BR, Kale BB. Mouth dissolving films: Innovative vehicle for oral drug delivery. polymer. 2013;2(10):41–47.
28. Thakur RR, Rathore DS, Narwal S. Orally disintegrating preparations: Recent advancement in formulation and technology. J Drug Delivery Ther. 2012;2(3).
29. Garg A, Gupta MM. Mouth dissolving tablets: A review. J Drug Delivery Ther. 2013;3(2):207–214.
30. Bhura N, Sanghvi K, Patel U, Parmar B. A review on fast dissolving film. The International Journal of Pharmaceutical Research and Bio-Science. 2012;1(3).

31. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: innovations in formulation and technology. Int J Pharm Sci Rev Res. 2011;9(2):50–57.
32. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth dissolving tablets I: An overview of formulation technology. Sci Pharm. 2009;77(2):309–326. doi: 10.3797/scipharm.0811-09-01.
33. Senthilkumar K, Vijaya C. Formulation development of mouth dissolving film of etoricoxib for pain management. Advances in Pharmaceutics. 2015;2015(1):702963. doi: 10.1155/2015/702963.
34. Shimoda H, Taniguchi K, Nishimura M, Matsuura K, Tsukioka T, Yamashita H, et al. Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. Eur J Pharm Biopharm. 2009;73(3):361–365. doi: 10.1016/j.ejpb.2009.08.010.
35. Zhao Y, Quan P, Fang L. Preparation of an oral thin film containing meclizine hydrochloride: In vitro and in vivo evaluation. Int J Pharm. 2015;496(2):314–322. doi: 10.1016/j.ijpharm.2015.10.008.
36. Cupone IE, Dellera E, Marra F, Giori AM. Development and characterization of an orodispersible film for vitamin D3 supplementation. Molecules. 2020;25(24):5851. doi: 10.3390/molecules25245851.
37. Patel P, Prajapati BG, Patel D. Mouth dissolving film as a potential dosage form for paediatric usage. Journal of Pharmaceutical and Biological Sciences. 2023;11(2):133–141. doi: 10.18231/j.jpbs.2023.021.
38. Chandramouli M, Shivalingappa RP, Basavanna V, Doddamani S, Shanthakumar DC, Nagarajaiah SR, et al. Oral thin-films from design to delivery: A pharmaceutical viewpoint. Biointerface Research in Applied Chemistry. 2022;13(2):177. doi: 10.33263/BRIAC132.177.
39. da Silva CF, Almeida T, de Melo Barbosa R, Cardoso JC, Morsink M, Souto EB, et al. New trends in drug delivery systems for veterinary applications. Pharm Nanotechnol. 2021;9(1):15–25. doi: 10.2174/2211738508666200613214548.
40. Ekpa ED, Asuquo UR, Elijah AA, Ime SN, Ini UA. The oral film delivery-Application of nanotechnology and potential in medication adherence. GSC Biological and Pharmaceutical Sciences. 2020;11(3):034–051. doi: 10.30574/gscbps.2020.11.3.0154.
41. Visser JC, Woerdenbag HJ, Hanff LM, Frijlink HW. Personalized medicine in pediatrics: The clinical potential of orodispersible films. AAPS PharmSciTech. 2017;18(2):267–272. doi: 10.1208/s12249-016-0515-1.
42. LaCoste A, Schaich KM, Zumbrunnen D, Yam KL. Advancing controlled release packaging through smart blending. Packaging Technology and Science. 2005;18(2):77–87. doi: 10.1002/pts.675.

