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Novel Advancements in Mouth Dissolving Film Technology

Nannar AR*, Khose R, Gaikwad R, Chaudhari R, Dhokare R, Karkande P, Rajashri G, Kandekar R, Khodade R and Kurpatwar B

Matoshri Miratai Aher College of Pharmacy, India

***Corresponding author:** Ajay Ramdas Nannar, Matoshri Miratai Aher College of Pharmacy, India, Tel: 8329282608, Email: ajaynannar@gmail.com

Review Article

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Abstract

Mouth dissolving film (MDF) technology has emerged as an innovative drug delivery platform offering rapid drug absorption and enhanced patient compliance. This comprehensive review explores recent advancements in MDF technology, focusing on formulation strategies, manufacturing techniques, and applications in pharmaceutical and nutraceuticals industries.

Key Topics Covered Include

1. Formulation Optimization: Novel excipients, such as water-soluble polymers, plasticizers, and taste-masking agents, are being explored to improve the mechanical properties, taste, and stability of MDFs. Advanced formulation techniques, such as hot-melt extrusion and solvent casting, allow for precise control over drug loading, release kinetics, and film characteristics.

2. Drug Delivery Enhancements: Integration of nanotechnology, such as nanoparticles and liposomes, enhances the solubility, bioavailability, and targeted delivery of poorly soluble drugs. Mucoadhesive polymers and permeation enhancers facilitate mucosal absorption, enabling faster onset of action and improved therapeutic outcomes.

3. Personalized Medicine: Customized dosing and patient-specific formulations are enabled by advancements in manufacturing technologies, including 3D printing and micro fabrication. Tailored MDFs address individual patient needs, preferences, and therapeutic requirements, promoting personalized medicine and optimizing treatment outcomes.

4. Combination Products: MDFs offer a versatile platform for the co-delivery of multiple drugs or therapeutic agents, enabling synergistic effects and simplified dosing regimens. Combination MDFs enhance treatment efficacy, reduce pill burden, and improve patient adherence, particularly in chronic disease management.

5. Regulatory Considerations: Regulatory guidelines and quality standards for MDF development and manufacturing are evolving to ensure product safety, efficacy, and reproducibility. Harmonization efforts facilitate global market access and encourage innovation in MDF technology.

Overall, the advancements in MDF technology are driving the development of patient-friendly, effective, and versatile drug delivery systems with broad applications in pharmaceuticals, nutraceuticals, and medical devices. Future research directions include targeted delivery strategies, biodegradable materials, and personalized formulations to address unmet clinical needs and enhance patient care.

Introduction

Mouth Dissolving films that are intended to dissolve in the mouth are known as mouth dissolving films. Although they can also be used to provide vitamins or minerals, medications are the usual usage for them. There are several materials used to make mouth dissolving films, such as hydroxypropyl methylcellulose, polyvinyl acetate, and cellulose acetate. Usually slender and malleable, they can be seasoned to enhance their flavor [1]. Because mouth

dissolving films are absorbed through the oral mucosa, they provide medicine in a quick and effective manner. Because they don't need water to ingest, they are also quite practical. Both over-the-counter and prescription options are available for mouth dissolving films [2].

Acetaminophen, nitroglycerin, and ibuprofen are a few typical drugs that come in mouth dissolving film form. A secure and efficient method of delivering medicine is by mouth dissolving films. They might not, however, be appropriate for everyone. For instance, oral dissolving films might not be suitable for use by those who suffer from certain medical problems, such as dry mouth [3]. Furthermore, for those with certain illnesses like gastroesophageal reflux disease (GERD), mouth dissolving films might not be as beneficial as alternative drug formulations like pills or capsules. The film is the perfect intraoral fast-acting medication delivery device [4].

Many medications, such as those for erectile dysfunction, analgesics, antihistamines, neuroleptics, cardiovascular medications, and analgesics, can be made as mouth dissolving films [5].

Due to its many advantages, rapid or quick dissolving oral thin films are becoming a more and more common drug delivery method. They are especially good for pediatric and elderly people since they dissolve in saliva in a matter of seconds without the need for water. Drug dispersion in the polymer matrix promotes quick dissolve since the majority of polymers used in mouth dissolving films (MDFs) are amorphous [6]. These benefits increase patient compliance and encourage pharmaceutical manufacturers to spend money switching out their current line of medications to MDFs. Because of its novelty, ease of administration, improved solubility, and subsequent patient compliance, mouth dissolving film (MDF) is a superior option than oral disintegrating tablets [7].

The films are meant to dissolve in a matter of seconds when they come into touch with a moist surface, such the tongue, so the user may swallow the product without adding more liquid. This simplicity of use boosts patient compliance and gives a marketing edge.

In order to provide a therapeutic or pharmacological impact, the mouth dissolving film (MDF) is frequently utilized for systemic drug delivery. MDF formulations bypass first pass metabolism, which improves systemic bioavailability. No need to drink water. Accessible in a range of forms and sizes [8].

The oral route is the most popular method for administering drugs since it is flexible, non-invasive, patient-acceptable, and easy to administer. When it comes to the oral route of medicine administration, several alternatives have been continually given for patients who are nauseated, elderly, juvenile, or noncompliant by using current innovative technology. Adhesive tablets, gels, and patches-among the bio adhesive mucosal dosage forms-are products of technical advancement [9]. The use of polymeric films, among other dosage forms, to transport medicine into the buccal cavity has shown a lot of promise recently. When applied to the tongue, mouth dissolving films release the active medicinal ingredient from the dosage form and instantly hydrate the saliva after dissolving and/or disintegrating [10].

Mouth dissolving films are a kind of formulation that are frequently made using hydrophilic polymers, which allow for quick dissolving in saliva. The most common types of oral disintegrating drug delivery methods are mouth dissolving tablets and mouth dissolving films (MDFs). These devices were created in the latter part of the 1970s as an alternative to traditional dose forms, such as fast-dissolving pills and capsules for young patients and the elderly who have trouble swallowing traditional dosage forms. An Mouth Dissolving Film is typically the same size as a postage stamp. When Mouth dissolving tablets was first introduced to the market, it was closely linked to patient education for proper administration, including instructions such as "do not chew/ do not swallow" [11].

Still, events involving swallowing and chewing were frequently reported despite these recommendations. The people were, however, freed from these negative occurrences by MDFs the following are only a few benefits of administering MDFs, among many others:

High mechanical strength, quick disintegration, low choking dangers, and no costly lyophilization are some of MDFs' qualitative characteristics. Due to its special qualities and quick disintegration period, which may be anywhere from a few seconds to a minute, ODFs have become extremely important in the pharmaceutical business. A range of medications, such as those with anti-tussive, anti-epileptic, anti-asthmatic, expectorant, and other pharmacological actions, can be included thanks to MDFs' design. One drawback of MDFs is that they cannot be used with large dosage loading due to their extreme sensitivity to moisture and temperature, which requires costly packaging [12].

Objective of Mouth Dissolving Films

The objectives of mouth dissolving films (MDFs) include

Rapid Drug Delivery

MDFs are designed to dissolve quickly upon contact with saliva, facilitating rapid drug absorption through the oral mucosa and achieving fast onset of action.

Improved Patient Compliance

MDFs offer a convenient and easy-to-administer dosage form that does not require water for swallowing, enhancing patient compliance, particularly for individuals with swallowing difficulties or aversion to traditional solid dosage forms.

Enhanced Bioavailability

By promoting drug absorption through the oral mucosa, MDFs can improve the bioavailability of poorly soluble drugs and reduce first-pass metabolism, leading to increased therapeutic efficacy.

Taste Masking

MDF formulations can incorporate taste-masking agents and flavoring agents to improve palatability and patient acceptability, especially for drugs with bitter or unpleasant tastes.

Customized Dosing

MDF technology enables precise control over drug loading and dose uniformity, allowing for customized dosing regimens tailored to individual patient needs and therapeutic requirements.

Versatility in Formulation

MDFs can accommodate a wide range of drug types, including small molecules, peptides, and proteins, as well as various functional additives, such as mucoadhesive polymers and permeation enhancers, to optimize drug delivery and performance.

Potential for Combination Products

MDFs provide a versatile platform for the co-delivery of multiple drugs or therapeutic agents in a single dosage form, offering synergistic effects, simplified dosing regimens, and improved treatment outcomes for various medical conditions.

Compatibility with Sensitive Drug Molecules

MDF formulations can be designed to protect sensitive drug molecules from degradation or denaturation, enhancing stability and shelf life.

Regulatory Compliance

MDF development aims to meet regulatory requirements for pharmaceutical products, ensuring product safety, efficacy, and quality throughout the manufacturing process and product lifecycle.

Overall, the objectives of MDF technology are to provide a patient-friendly, effective, and versatile drug delivery platform that addresses unmet clinical needs, enhances patient care, and improves medication adherence.

Current Scenario of Mouth Dissolving Films

A growing number of people are using rapid or quick dissolving oral thin films as a medicine delivery method due to its many great advantages. Because it dissolves in saliva quickly and doesn't require water, it's especially good for elderly and pediatric patients. The medicine is dispersed in the polymer matrix to facilitate quick dissolve, as most of the polymers used in mouth dissolving films (MDFs) are amorphous. Pharma manufacturers are compelled to spend in switching from their current products to MDFs due to these advantages, which also improve patient compliance [13].

One of the most popular ways to administer drugs is orally as it is more practical, affordable, and leads to high levels of patient compliance. The oral route is a challenge for elderly and pediatric patients who have trouble swallowing and are afraid they may choke. Newer and safer medication delivery methods have been introduced as a consequence of research focused on patient convenience and compliance. Because they dissolve quickly and allow for self-administration without the need for water or chewing, fast dissolving medication delivery systems have become more and more popular and accepted as one example of a system that offers consumers more choice [14].

Advantages of Mouth Dissolving Film

1. Convenient dosing.
2. No water needed.
3. No risk of chocking.
4. Taste masking.
5. Enhanced stability.
6. Improved patient compliance.
7. The drug enters the systemic circulation with reduced hepatic first pass effect.
8. Site specific and local action.
9. Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
10. Dose accuracy in comparison to syrup.
11. Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability.

Disadvantages 0f Mouth Dissolving Film

1. Drugs which are unstable at buccal pH cannot be

administered.

2. Drugs which irritate the mucosa cannot be administered by this route.
3. Drug with small dose requirement can only be administered.
4. Taste masking- Most drugs have bitter taste, and need taste masking.
5. Special packaging- MDFs are fragile and must be protected from water so it needs special packaging.
6. Dose uniformity is a technical challenge
7. Expensive packaging of oral film.
8. High dose cannot be incorporated into the oral film.
9. It is hygroscopic in nature so it must be kept in dry places.

Formulation

In the formulation of mouth dissolving films up to 15 mg of the active pharmaceutical component may be added with various excipients, such as plasticizers, colorants, sweeteners, flavor masking agents, etc. Plasticizer lowers the glass transition temperature of polymers by improving the workability, spread ability, and flexibility of films [15].

- Composition of a typical ODF.
- Components Conc. (%)
- Active pharmaceutical ingredient 1–25
- Hydrophilic polymer 40–50
- Plasticizer 0–20
- Color, filler, flavor 0–40

Active Pharmaceutical Ingredient

Anti-histamine, anti-diarrheal, anti-depressant, vasodilator, anti-asthmatic, anti-emetic, and other medication classes are among those that can be included in MDFs. For the purpose of disguising flavor, MDFs can also contain dimenhydrinate. Many medications, such as salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc., are frequently included in MDFs. Microcrystalline cellulose and other film-forming polymers were also used to create an MDF of an anti-emetic drug similar to prochlorperazine [16].

Hydrophilic Polymers

The appropriate choice and concentration of polymers are essential for the effective formation of an MDF since these parameters are closely linked to the mechanical strength of the films. To change the characteristics of films, they can be applied singly or in conjunction with other polymers. While creating an MDF, the concentration of the polymers being employed is also crucial. The kind and concentration of the polymer must be carefully chosen to ensure the integrity of quickly disintegrating oral films. In order to achieve the appropriate features and properties for the film, the polymer concentration employed in the preparation of MDFs can be raised up to 60–65% w/w of the total weight of dry thin strip. This concentration is typically about 45% w/w. certain qualities are required of the polymer utilized as a film-forming agent in the formulation of thin strips [17].

Ideal Properties of Hydrophilic Polymers

- Properties
- Not irritating
- Should not impede the MDF's disintegration time
- Reasonably priced
- Should have decent spread ability, a suitable tensile strength, and acceptable mechanical qualities. It should also have an appropriate shelf life.
- Not harmful
- Not irritating
- Both synthetic and natural polymers are now employed in the development of ODF formulations.

Most Commonly Used Natural and Synthetic Polymers in ODFs

Type of polymer and examples

- Natural - Starch, polymerized rosin, pullulan, sodium alginate, Pectin, gelatin, and maltodextrins
- Synthetic- Polyvinyl alcohol, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, polyvinyl pyrrolidone, and hydroxy propyl cellulose.

To modify the various characteristics of films, several polymers are utilized. Films containing pullulan offer strong tensile strength and stability across a wide temperature range, in addition to pullulan's enhanced solubility. The qualities of produced films are influenced by the molecular weights of the gelatins used. A film that is notably more attractive may be achieved by utilizing polymers with an average molecular weight that are higher [18].

Superior quality strips are produced when chitosan and either low methoxy pectin (LMP) or high methoxy pectin (HMP) are combined. Owing to their hydrophilic nature, cellulose-derived film-forming polymers, such as carboxymethyl cellulose (CMC), methyl cellulose (MC), hydroxypropyl cellulose (HPMC), and hydroxypropyl cellulose (HPC), produce films with a lower water vapor barrier. When combined with other polymers or used alone, polyethylene glycol (PEG) possesses strong film-forming qualities as well [19].

Various grades, such as Methocel E3, Methocel E5, and Methocel E15 Premium LV, are available from HPMC, which

is an excellent film former. It was shown that Methocel E15 Premium LV produced films with the right qualities when triclosan was developed into a fast-dissolving film using various grades of HPMC. Quick-dissolving famotidine film made with polyethylene glycol (PEG) and HPMC showed the intended physico-chemical characteristics. Fast dissolving films were made with maltodextrins (MDX) and an equal low dosage of dextrose, and a water-insoluble medication called piroxicam was added. Changes in polymer content have a significant impact on both mechanical characteristics and drug release percentage, as demonstrated by ODFs of nebivolol HCl produced from HPMC, pullulan, and polyvinyl pyrrolidone (PVP) [20].

Mono- and double-layered chlorhexidine buccoadhesive films were developed to illustrate the fact that polymers control the release profile. Films produced with alginate, HPMC, and/or chitosan improved drug release. The mechanical characteristics and film strength were demonstrated by the granisetron hydrochloride ODFs, which were produced using pullulan and HPMC, contrasting the impact of polymer concentration. While films with up to 40% HPMC content were difficult to peel, films with pullulan concentrations of 40–45% did not produce films with high qualities. Furthermore, at concentrations greater than 50%, the stickiness of the film increased [21].

An investigation into the production of fast-dissolving films of losartan potassium using varying quantities of polyvinyl alcohol (PVA) and maltodextrins (MD) revealed a clear relationship between increasing polymer concentration and in vitro disintegration time [22].

Plasticizers

Plasticizer is generally added to formulations to increase mechanical qualities including tensile strength and % elongation. Plasticizer concentrations typically fall between 0% and 20% w/w. PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, etc. are typical examples of plasticizers.

Surfactants

Surfactants are essential because they function as dispersing, wetting, and solubilizing agents. This allows films to break down quickly and release the integrated medication. Benzalkonium chloride, tweens, and sodium lauryl sulfate are examples of surfactants that are often utilized. Poloxamer 407 is frequently utilized because of its various benefits.

Flavor

Incorporated drugs have an unpleasant or bitter taste that needs to be covered up with flavors. Its type and strength determine how much taste it has. Any flavor-such as sweet, sour, or mint-that has been approved by the US FDA may be utilized. Research has confirmed that the tastes of mint, licorice, and sucralose combination effectively conceal the bitter taste of diclofenac sodium. To distinguish between different tastes masking agents' effects, electronic tongues are utilized (TMAs).

Sweetening agents

Sweetening agents are designed to disintegrate or dissolve in oral cavity. Both artificial and natural sweeteners are used in preparing ODFs.

Sweetening agent

Example

Natural - Glucose, fructose, dextrose, sucrose, and isomaltose

Artificial- Acesulfame-K, sucralose, and neotame

Compared to sucrose, neotame and alitame are 2000–8000 times sweeter. Compared to sorbitol and mannitol, fructose has a greater ability to sweeten. When oral disintegrating films of donepezil were assessed for taste, mouth feel, and sweetness, it was discovered that sucrose was 600–1000 times sweeter than sucrose. Comparing aspartame and saccharin sodium to sucrose, they should be 200–500 times sweeter, respectively. Additionally, it was stated that tastes and sweeteners had no impact on the film's elasticity.

Saliva stimulating agent

The majority of salivary stimulants have an acidic quality, which causes them to increase saliva production in the buccal cavity and aid in the disintegration of ODFs. Citric acid, tartaric acid, malic acid, ascorbic acid, and lactic acid are a few often utilized saliva-stimulating substances.

Coloring agents

Colorants are derived from pigments. In ODFs and other pharmacological formulations, titanium dioxide is the colorant most frequently utilized. In addition to titanium dioxide, a wide variety of hues are offered, such as FD and C, natural, and specially blended pantone matches.

Manufacturing Techniques of Mouth Dissolving Films

Mouth dissolving films are produced using a variety of techniques, including rolling, solvent casting, hot-melt extrusion, semisolid casting, and solid-dispersion extrusion. The writers go over these techniques as well as the many metrics used to assess dissolving films.

When applied to the tongue, oral thin films, also known as Mouth dissolving films (MDFs), offer an active pharmaceutical

ingredient (API) with rapid release. Orally disintegrating tablets have an alternative in the form of MDFs. The patient applies these dose forms on their tongue or other oral mucosal tissue. Saliva quickly hydrates the film and causes it to stick to the application location. It dissolves and disintegrates quickly, releasing the medication for mucosal absorption or-with some modifications—allowing for oral gastrointestinal absorption with fast-acting dissolve ability [23].

Originally, these films were marketed as mouthwashes with thymol and menthol in them. These films are offered as breath-freshening products by Boots (Nottingham, UK), Wrigley (Chicago), and Johnson & Johnson (New Brunswick, NJ) in the United States and Europe. In the US, Zengen (Woodland Hills, CA) manufactures a chloraseptic relief strip that contains benzocaine, a local anesthetic used to treat sore throats [24].

These ODFs include film-forming polymers such sodium alginate, pectin, starch, carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), and hydroxypropyl cellulose (HPC). Plasticizers, coloring, thickening, saliva-stimulating, sweetening, and flavoring agents are among the other substances that are added. Fast dissolving films can be used as transdermal nicotine replacement therapy, as well as antihistamine and anti-ulcer medications. Prescription medications for sleeping disorders and antipsychotics are potentially possible options.

ODFs provide several benefits, such as enhanced mobility, simplicity in administration, precise dosage, economic viability, and better patient adherence [25].

Manufacture of MDFs

Heat-melt extrusion (HME), rolling, solvent casting, semisolid casting, and solid-dispersion extrusion are processes that can be employed alone or in combination to create MDFs. The two most popular processes for making films are HME and solvent casting [26].

The solvent-casting technique. Preferably, the solvent-casting process is used to formulate the MDF, dissolving the water-soluble components to create a transparent, viscous solution. Smaller quantities of the API and other agents are dissolved in the solution and mixed in with the bulk medication. The watery, viscous solution receives this combination added to it. A vacuum is used to release the trapped air. To achieve homogeneous film properties and thickness, desecration is required. The final mixture is poured into a film, given time to dry, and then divided into the required size pieces. The choice of an appropriate solvent is greatly influenced by the characteristics of the API [27].

The API's physicochemical characteristics have to be taken into account. These characteristics include the API's temperature sensitivity, compatibility with solvents, compatibility with other film-forming excipients, and polymorphism. MDFs must be manufactured and packaged with extra care to regulate the impact of moisture. The presence of moisture considerably affects the film's mechanical characteristics and stability. Temperature is another element that needs to be well regulated. The viscosity of the solution and the API's temperature sensitivity must be maintained under controlled temperature settings [28].

Pouring the solution over an inert foundation requires specialized tools, including rollers. The necessary film thickness is determined by the space between the roller and the substrate. The last stage, drying the film, assists to produce the final result by getting rid of the solvent. Film casting often uses glass, plastic, or Teflon plates as an inert basis. A number of issues might arise when manufacturing technology is moved from the lab to the production level. These issues may involve the casting of the film, achieving a consistent film thickness, and appropriately drying the sample. The last stage of drying requires choosing the right kind of drier [29].

After the films have dried, they are cut, stripped, and packaged. Films with the right dimensions and forms can be cut. Films are often available in two and three-by-two-centimeter diameters. A criteria for the MDF that is equally significant is the choice of packing container. Enough mechanical strength should be provided by the packaging container to shield the film from the elements and from shipping-related stresses like humidity and temperature. Single-unit containers and multiple-unit dispensers can be chosen based on the features of the film. Prior to being placed inside a secondary packing container, the packaged films are examined [30].

Extrusion using a hot melt. Granules, sustained-release pills, and transdermal and transmucosal drug delivery devices are frequently made using HME. The pharmaceutical sector has lately seen a rise in the use of the HME procedure. Formulators can generate desired drug-release profiles by extruding mixtures of medicines, polymers, and plasticizers into different final forms, based on information from the plastics industry. Using this method of processing films, a polymer is shaped into a film by heating it instead of using the conventional solvent-casting approach [31].

Advantages of HME for Film Formation Include the Following

- No need to use water or a solvent

- Fewer stages in the processing
- The API's compressibility characteristics might not be significant.
- Effective dispersion method for poorly soluble medications
- Because of the vigorous mixing and agitation, the tiny particles were more evenly dispersed.
- Using less energy than high-shear techniques
- Minimal amount of product waste
- Potential for scaling up
- Good management of the parameters of operation.

Melting the material into a liquid form and pushing it out of the hot-melt extruder are the steps in the HME process. The procedure begins with mixing the API and other excipients in a dry condition. The total solvent removal provided by this technique is its benefit. After cooling, the films are trimmed to the appropriate length. It is appropriate for medications that are thermo stable due to the elevated temperature used in the procedure. This procedure prohibits the use of drugs that are temperature sensitive [32].

Unlike HME, which needs thermos table pharmaceuticals and is anhydrous, solvent casting is a hydrous method that may be used with thermo labile and thermo stable medications. The effects of topical HPC films by HME were investigated by Repka et al. using chlorpheniramine maleate (CPM) (5). According to reports, CPM acts as a potent plasticizer that concentration-dependently increases % elongation and decreases tensile strength. Because CPM permits film processing at lower temperatures, it also serves as a processing aid for hot-melt film extrusion [33].

Examining HPC films with seven polymer additions in vivo and their in vivo bioadhesive qualities on human subjects' epidermis was done (7). HME produced additive-containing HPC films both with and without plasticizers. HPC films' bio adhesion was greatly enhanced by the addition of polycarbophil and a carbomer (Carbopol 971P NF, Lubrizol, and Cleveland, OH). Utilizing HME to produce solid dispersions was the subject of several investigations. Amorphous solid-solutions were found to occur when miscible components were melt extruded, but crystalline excipients produced amorphous drug dispersion when immiscible components were extruded [34].

Solid dispersions may be made using this method in a single step. An extruder is made up of two separate components. A conveyer system that moves the material and applies some distributive mixing makes up the first section. A dye system, the second component, shapes the materials into the desired shape. The extruder conveys, mixes, and melts the drug-carrier mix once it has been filled in the hopper. The melt is shaped by the die into the desired shape, such as films, granules, pellets, or powder, which can then be processed further to create regular tablets or capsules. For materials that are prone to oxidation and hydrolysis, all oxygen and moisture should be removed [35].

Semisolid Casting

A solution of the film-forming, water-soluble polymer is made using the semisolid-casting technique. A solution of acid-insoluble polymer (such as cellulose acetate phthalate and cellulose acetate butyrate) that has been previously produced in sodium or ammonium hydroxide is combined with the final solution. A gel mass is produced by adding the proper quantity of plasticizer. A regulated heat source is used to cast the prepared gel mixture into films or ribbons. The film's thickness is regulated within a range of 0.015–0.05 inches.

Solid-Dispersion Extrusion

When one or more APIs are dispersed using techniques like HME in an inert carrier in a solid state with amorphous hydrophilic polymers present, the process is referred to as solid dispersion. Solid dispersions are created by extruding immiscible components with medication in a process known as solid-dispersion extrusion. Dies are used to form the solid dispersions into films. A appropriate liquid solvent is used to dissolve the medication. Without eliminating the liquid solvent, this solution is added to the melt of polyols, such as polyethylene glycol, that is produced below 70 °C. It's possible that the chosen solvent or medication solution won't mix well with the polyethylene glycol melt. The liquid solvent utilized may have an impact on the drug's polymorphic form that precipitated in the solid dispersion [36].

Rolling Method

The rolling method involves rolling a drug-containing solution or suspension on a carrier. The solvent mostly consists of water and a water-alcohol combination. The film is trimmed to the appropriate size and form after being dried on the rollers. Film is created by mixing the API into a premix and then forming the film. The film-forming polymer, polar solvent, and other excipients—aside from the API—found in the premix or master batch are fed to the master-batch feed tank. Through the use of a control valve and metering pump, a preset volume of the master batch is delivered to the mixers. The intended mixer has an entrance via which the necessary quantity of the medicine is introduced.

Measuring pumps are used to feed the uniform matrix to the pan after the API and master batch have been blended. A metering roller is used to manage the film's thickness. Finally, the film forms on the substrate and is removed by the

support roller. Controlled bottom drying is used to dry the wet film, ideally without the presence of heat or air currents from the outside.

Evaluation of the MDF

Numerous factors are taken into consideration while evaluating the ODF, including its thickness, mechanical qualities, folding durability, assay/drug content, and investigations conducted on its surface morphology, taste, and in-vitro disintegration and dissolution.

The Thickness

A micrometer can be used at several spots to measure the thickness of the strip. The precision of the dosage in the strip is closely correlated with the thickness of the film, thus this measurement is crucial to determining the uniformity of the thickness. the film's mechanical characteristics. Elastic modulus, percentage elongation, and tensile strength are the mechanical properties.

Tensile Strength

The greatest stress given to a strip specimen before it breaks is known as its tensile strength.

Percentage Elongation

A film sample expands when tension is applied; this stress is known as strain. In essence, strain is the film's distortion divided by the sample's initial dimension. The film is shown to elongate as the plasticizer concentration rises.

Resistance to Tears

A plastic film's ability to withstand tears is intricately linked to its eventual ability to withstand ruptures. 51 mm/min, an extremely slow loading rate, is used. Its purpose is to gauge the amount of power needed to start ripping. The rip resistance in newton's is defined as the greatest stress or force—typically obtained close to the beginning of tearing—necessary to tear the specimen.

Elastic Modulus, also known as Young's Modulus

The rigidity of the film is gauged by its elastic modulus, also known as Young's modulus. It may be expressed as follows: the ratio of applied stress to strain in the elastic deformation zone
Brittle and hard strips show reduced % elongation and a high Young's modulus and tensile strength.

Endurance in Folding

The film is repeatedly folded in the same spot until it breaks to determine the folding durability of the film. The folding endurance value is determined by counting the folds of the film without breaking. Drug content or assay. Assay/drug content is ascertained using any standard assay technique specified in any standard pharmacopoeia for the specific API.

In-Vitro Disintegration

The film's disintegration and dissolution features may be inferred from the disintegration time. In this investigation, the film was laid out according to the measurements needed to administer the dosage on a stainless steel wire mesh that held 10 milliliters of deionized water. The in-vitro disintegration time was defined as the amount of time needed for the film to shatter [37].

In Vitro Dissolution

Because a regular paddle apparatus may cause the film to float, in-vitro dissolving investigations can be carried out utilizing the modifications to the usual basket or paddle apparatus stated in any of the pharmacopoeia. The greatest dosage of API and the sink conditions will be taken into consideration while choosing the dissolving media.

Surface Morphology

Using environment-scanning electron microscopy, the surface morphology of the ODF is studied. The ODF's high quality is shown by the film's homogeneity and the lack of holes and striations.

Taste Evaluation

A panel of human volunteers may be used in a research evaluating taste. The ideal sweetness and taste that the patient finds acceptable should be included in the ODF. This is accomplished using in vitro techniques that make use of taste sensors, a specifically made device, and drug release by adapted pharmacopoeial techniques. Studies employing electronic tongue measurements have also been documented to differentiate between the degrees of sweetness in taste-masking formulations [38].

Characterization of MDFs

Many investigations and measurements are performed as part of the characterization studies of the produced OTFs. These include the following: degree of transparency; X-ray powder diffraction (XRD), X-ray electron microscopy

(SEM), fourier transform infrared spectroscopy (FT-IR), and differential scanning calorimetry (DSC) analyses and measurements; moisture absorption; swelling ability; flexibility (elongation); folding ability; pH determination; weight variability; thickness; flavor; content uniformity; dispersion; dissolution rate; release kinetics; and degree of transparency.

MDFs are challenging to differentiate because of the brief durations of the disintegration and dissolution processes. The disintegration test can be used instead of the dissolution test for ODTs, according to the American Association of Pharmaceutical Scientists/International Pharmacy Federation. The pace at which API is released as the film dissolves depends only on whether the API is molecularly dissolved in OTF. The dissolving rate and disintegration time tests are also advised if the API is distributed in a particulate form in the film matrix. The FDA and USP (American Society for Pharmaceuticals) advise that ODTs dissolve in 30 seconds or less, despite the European Pharmacopoeia allowing up to three minutes for this process.

Since the saliva volume in the mouth is less than 2 mL, these tests are generally recommended in a small environment for disintegration testing in 2-7 mL of fluid under similar conditions prevailing in the oral cavity. OTF can be placed on the surface of the liquid in a petri dish, and the disintegration time can be determined utilizing a chronometer. In the meantime, the petri dish can be shaken continuously to mimic the tongue's mouth movement. This method is simple and offers ease of application. Otherwise, it creates some difficulties, and the process is very difficult to apply to automation.

According to the pharmacopoeia's guidelines for solid oral dosage forms, drug release from MDFs is typically conducted using a pallet or basket device in an environment with a temperature of 37°C (artificial saliva fluid or a pH 6.8 phosphate buffer). On the other hand, MDFs have several drawbacks with the dissolving equipment. In contrast, while using the pallet apparatus, MDFs are likely to stay to the bottom of the container in the dissolving liquid or remain on the top. While utilizing the basket apparatus, this might lead to adhering to the edges and clogging of the basket pores. To mimic adherence in vivo and inhibit swimming, platinum and double-sided tapes are employed. Each film is fastened to the bottom of the dissolving media and set on a rectangular glass plate. The medication is released extremely quickly as a result of the fast disintegration, and specimens of the examined medium are taken quickly.

Using a dissolving test device, the taste-masking characteristics of MDFs may be assessed in vitro. The safest method of testing is in vivo, however using volunteers has ethical challenges. Prior to the experiment, participants' sensory sensitivity thresholds are measured against four reference materials and tastes. These tastes are tartaric acid (sour), quinine (bitter), sucrose (sweet), and sodium chloride (salty). Using pure water, the volunteers first cleanse their lips. After that, they put a film specimen with the same dosage of drug and a quantity of pure drug on their tongues for 30 seconds each. The volunteers then rinse their lips with water after spitting. After that, they are put through a taste evaluation procedure that has three rating levels: 0 for tasteless, 1 for somewhat bitter, 2 for moderately bitter and 3 for extremely bitter.

Numerous research on OTFs' usage as stand-ins for commercially available conventional medications in the treatment of a variety of disorders have been published in the literature. The following APIs were used in these studies: cinitapride hydrogen tartarate, meloxicam, escitalopram, phenylephrine HCl, ondansetron HCl, fluticasone propionate, ergotamine, zolpidem tartrate, bufotenine, etoricoxib, levocetirizine dihydrochloride, leukotriene receptor antagonist, meloxicam, escitalopram, ergotamine, fluticasone propionate, and caffeine.

Clinical and Regulatory Requirement

A shortened new drug application is necessary to show a product's bioequivalency to an oral medication that is currently on the market. Considerations include therapeutic equivalency and in vitro dissolution tests. An oral disintegrating tablet and an ODF can be compared for comparative bioequivalency. A novel dosage form is identified in the event that the ODF has a distinct target pharmacokinetic profile from the already marketed medication. One further clinical research is needed for a new dose type. A three-year marketing exclusivity period for the product is provided by a recent clinical trial. In the event if the molecule is identical to that of the authorized medication, preclinical toxicity studies are not needed. Such trials are intended to demonstrate qualities related to safety, tolerability, and effectiveness. Testing on oral mucosa is done on both people and animal models. The best model to predict irritation criterion prior to human testing is the hamster-cheek pouch.

Challenges that are faced during Formulation of Mouth Dissolving Films

1. A medication solubility-related issue.
2. For the unpleasant medications, a specific flavor masking agent is needed.
3. The inability to maintain dose consistency.
4. The financial difficulties associated with organizing the packing supplies.
5. Issues with medication storage that compromise content preservation.

Novel Advancements in Mouth Dissolving Film Technology

Mouth dissolving film (MDF) technology has seen significant advancements in recent years, with ongoing research focusing on several key areas:

Enhanced Drug Delivery

Researchers are exploring ways to improve the dissolution rate and bioavailability of drugs through MDFs, allowing for faster absorption and onset of action.

Formulation Optimization

Novel formulations are being developed to enhance the mechanical properties, stability, and taste-masking capabilities of MDFs, ensuring patient compliance and acceptability.

Functional Additives

Incorporating functional additives such as mucoadhesive polymers, permeation enhancers, and taste-masking agents can further improve the performance and patient experience of MDFs.

Customized Dosing

Advances in manufacturing techniques enable the precise control of drug loading and dose uniformity within MDFs, facilitating personalized medicine and tailored dosing regimens.

Novel Manufacturing Methods

Innovations in manufacturing processes, such as 3D printing and micro fabrication, are being explored to create MDFs with customizable shapes, sizes, and drug release profiles.

Combination Products

Researchers are investigating the feasibility of incorporating multiple drugs or therapeutic agents into single MDF formulations, offering synergistic effects and improved treatment outcomes for various medical conditions. Overall, these advancements are driving the development of MDFs as a versatile and patient-friendly drug delivery platform with broad applications in pharmaceuticals, nutraceuticals, and medical devices.

One novel development in mouth dissolving film (MDF) technology is the integration of nanotechnology to enhance drug delivery. Nanoparticles, such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles, can be incorporated into MDF formulations to improve the solubility, stability, and bioavailability of poorly soluble drugs. These nanoparticles can encapsulate the drug, protect it from degradation, and facilitate its absorption through the mucosal membranes in the oral cavity, resulting in faster onset of action and improved therapeutic outcomes. Additionally, nanotechnology allows for the targeted delivery of drugs to specific tissues or cells, minimizing systemic side effects. This integration of nanotechnology with MDFs represents a promising approach to optimize drug delivery and expand the application of MDFs in various therapeutic areas.

One novel technology in mouth dissolving films (MDFs) is the use of 3D printing. This advanced manufacturing method allows for precise control over the composition, structure, and drug distribution within the MDFs. By using 3D printing, it's possible to create customized MDFs with complex geometries, tailored drug release profiles, and even multi-layered structures. This technology offers advantages such as rapid prototyping, scalability, and the ability to incorporate multiple drugs or functional additives in a single dosage form. Additionally, 3D printing enables the creation of patient-specific MDFs, facilitating personalized medicine and improving treatment outcomes. Overall, the integration of 3D printing technology into MDF production represents a significant advancement in drug delivery systems, offering enhanced precision and versatility in formulation design.

Comparison between Mouths Dissolving Tablets vs Mouth Dissolving Films

Mouth dissolving tablets (MDTs) and mouth dissolving films (MDFs) are both innovative dosage forms designed to disintegrate rapidly in the oral cavity, providing quick drug delivery without the need for water. Here's a comparison between the two:

Physical Form

MDTs are solid dosage forms, typically made using direct compression or lyophilization techniques. They often contain super disintegrates to facilitate rapid disintegration upon contact with saliva. On the other hand, MDFs are thin, flexible films that quickly dissolve in the mouth. They are typically composed of water-soluble polymers and other excipients.

Drug Loading and Dosage Flexibility

MDTs can accommodate a wide range of drug types and doses, but they may have limitations in terms of high-dose or large-molecule drugs due to formulation challenges.

MDFs offer more flexibility in drug loading and can easily accommodate both small and large molecule drugs. They also allow for precise dosing, making them suitable for pediatric and geriatric populations.

Ease of Administration

Both MDTs and MDFs are easy to administer and do not require water, making them convenient for patients with swallowing difficulties, pediatric patients, or those on the go. However, MDFs may offer slightly better ease of administration as they are thin films that can be placed on the tongue without the need to swallow.

Taste-Masking and Patient Acceptance

Both dosage forms can be formulated to mask the taste of bitter or unpleasant drugs, enhancing patient acceptance and compliance. However, MDFs may offer better taste-masking properties due to the ability to incorporate flavoring agents directly into the film matrix.

Stability and Shelf Life

MDTs generally have better stability and longer shelf life compared to MDFs, which may be more susceptible to moisture and environmental factors. However, advancements in MDF formulation and packaging technology are improving their stability over time.

Manufacturing Complexity

MDTs typically require conventional tablet manufacturing equipment and processes, which may be simpler and more cost-effective compared to MDFs. MDFs, may require specialized equipment and expertise for manufacturing, such as casting or extrusion techniques.

Overall, both mouth dissolving tablets and mouth dissolving films offer unique advantages and are valuable options for patients who require rapid drug delivery or have difficulty swallowing traditional dosage forms. The choice between the two depends on factors such as the drug properties, patient preferences, and manufacturing considerations.

New Mouth Dissolving Films

Several recent developments and innovations have emerged in the field of mouth dissolving films (MDFs), showcasing advancements in formulation, manufacturing, and applications. Here are some notable examples of new MDF technologies:

Nanotechnology Integration

Researchers are exploring the incorporation of nanoparticles, such as liposomes and polymeric nanoparticles, into MDF formulations to enhance drug solubility, bioavailability, and targeted delivery. These nanocarriers protect the drug from degradation and facilitate its absorption through the oral mucosa, leading to improved therapeutic outcomes.

3D Printing Technology

The utilization of 3D printing technology enables the fabrication of MDFs with precise control over drug loading, release kinetics, and dosage form characteristics. This personalized manufacturing approach allows for the creation of patient-specific MDFs with customized shapes, sizes, and drug release profiles, enhancing treatment efficacy and patient adherence.

Multilayered Films

Novel MDF formulations with multilayered structures are being developed to achieve controlled drug release and sequential delivery of multiple drugs or therapeutic agents. These multilayered films offer versatility in drug combination therapy and enable tailored dosing regimens for various medical conditions.

Natural Polymers and Excipients

There is growing interest in the use of natural polymers and excipients, such as alginate, chitosan, and starch, in MDF formulations to enhance biocompatibility, biodegradability, and sustainability. These natural materials provide an alternative to synthetic polymers and offer potential benefits in terms of safety and environmental impact.

Functional Additives

The incorporation of functional additives, such as mucoadhesive polymers, permeation enhancers, and taste-masking agents, further enhances the performance and patient acceptability of MDFs. These additives improve the adhesion of MDFs to the oral mucosa, facilitate drug absorption, and mask the taste of bitter or unpleasant drugs, enhancing overall patient experience.

Regulatory Considerations

Efforts are underway to establish regulatory guidelines and quality standards specific to MDFs, ensuring product safety, efficacy, and quality throughout the development and manufacturing process. Regulatory agencies are working

closely with industry stakeholders to address challenges and streamline the approval process for MDF-based pharmaceutical products.

Overall, these new advancements in mouth dissolving film technology demonstrate the ongoing innovation and potential of MDFs as a versatile and patient-friendly drug delivery platform with broad applications in pharmaceuticals, nutraceuticals, and medical devices.

Conclusion

In conclusion, mouth dissolving films (MDFs) represent a promising drug delivery system offering numerous advantages such as ease of administration, enhanced patient compliance, rapid onset of action, and improved bioavailability. The development of MDFs involves careful selection of film-forming polymers, plasticizers, taste-masking agents, and active pharmaceutical ingredients, along with optimization of formulation parameters to achieve desired characteristics such as rapid disintegration, stability, and drug release profile. Various techniques such as solvent casting, hot melt extrusion, and spray drying are employed for the fabrication of MDFs. Furthermore, the incorporation of novel excipients, nanotechnology, and advanced manufacturing methods continues to enhance the performance and versatility of MDFs. Overall, MDFs hold great potential for delivering a wide range of drugs, including those intended for systemic absorption, local action, and pediatric or geriatric populations, thereby contributing to improved therapeutic outcomes and patient convenience. Further research and development efforts are warranted to explore new formulations, improve manufacturing processes, and address regulatory considerations to fully harness the benefits of MDFs in clinical practice.

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