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Fast Dissolving Oral Thin Films: A Review

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Abstract

Fast-dissolving oral thin films (FDOFs) represent a significant advancement in drug delivery technology, offering advantages over traditional solid dosage forms, especially for patients with swallowing difficulties. FDOFs dissolve rapidly in the mouth, releasing the active ingredient without the need for water or chewing. They have picked up ubiquity due to their comfort, taste veiling capabilities, and progressed persistent compliance. Ideal drugs for FDOFs should possess characteristics such as solubility, stability, and compatibility with oral mucosal tissue. Various drug categories, including anti-emetics, serotonin inhibitors, anti-epileptics, anti-migraines, and statins, can be formulated as FDOFs. Formulating FDOFs involves considerations like selecting appropriate polymers, plasticizers, flavoring agents, and colorants. Methods of preparation include solvent casting, semi-solid casting, hot-melt extrusion, solid dispersion, and rolling methods. Evaluation methods ensure quality control, covering aspects like weight uniformity, thickness, dryness, surface pH, tensile strength, disintegration time, and in-vitro drug release studies. Recent developments in FDOFs extend their applications to pain relief, CNS diseases, wound care, and controlled release of sensitive reagents. Despite their advantages, challenges remain in formulation, manufacturing, and market competition. In conclusion, FDOFs offer a promising drug delivery platform with broad applications and benefits, although further research and optimization are necessary to address existing challenges and realize their full potential in modern pharmaceuticals.

Keywords: Fast-dissolving films, polymers, solvent casting method, fast-dissolving tablets, orally disintegrating films

INTRODUCTION

Oral communication is the most convenient and preferred transmission method. Oral medication delivery systems account for over 70% of the market owing to their pain-free and versatile nature. Dysphagia was prevalent in all age groups. Approximately 50% of the population, particularly juvenile and geriatric patients, avoid taking solid oral dosages due to fear of choking. In the early 19th century, fast-dissolving tablets (FDTs) were used to address swallowing issues. As technology advances, Fast Dissolving Films (FDFs) have been produced. Fast-dissolving dose forms have gained popularity because of their unique features. These tablets break up quickly and do not require water, making them ideal for use in pediatric and geriatric patients. Fast-dissolving oral thin films (FDOFs) are widely utilized in different markets, including breath strips, individual care, nourishment, and medication conveyance [1]. Fast-dissolving oral thin films are ultra-thin films that utilize a hydrophilic polymer to rapidly hydrate or follow when placed on the tongue or within the buccal depth. These films crumble or dissolve within seconds, releasing the active ingredient without the

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need for drinking or chewing. Immediate bioavailability is achieved by bypassing first-pass metabolism. Therefore, they are often created for medications that have a high first-pass metabolism to achieve higher bioavailability [2]. There is a considerable specific surface area for the degradation of FDFs. Films reduce the risk of choking, are straightforward to administer, and offer easy-to-manufacture packaging, making them a viable alternative to fast-disintegrating oral pills. These dosage forms have minimal drug loading capacity and weak taste masking capabilities, which are significant downsides Fast dissolving films are thin films in any geometry that have an area of 1–20 cm2 and a thickness of 1–10 mm. Up to a single dose of approximately 30 mg, medications should be mixed. Saliva dissolves quickly because of its water-soluble polymer matrix with little tack, making it easy to apply [3]. According to Catalysts, the market for medical products in oral thin-film formulations was estimated at $500 million in 2007 and might reach $2 billion by 2012. The rapidly dissolving dose industry is expected to generate $13 billion in sales by 2015 based on global growth trends over the past decade. FDF technology is seen as an alternative to FDT products, providing a higher barrier to generic entry and distinctiveness from over-the-counter brands. Patented orally disintegrating films (ODFs) technology may help advertising campaigns. Providing a new dosage form of marketing exclusivity would boost sales. FDFs are also known as mouth-dissolving films (MDFs), orally disintegrating films, melt-in-mouth films, oro-dispersible films, and quick-dissolving films (Table 1).

IDEAL CHARACTERISTICS OF A DRUG FOR ORAL FILMS

- The drug should have a pleasant flavor. The drug should have a small molecular size and weight.
- The drug should be soluble and stable in both water and saliva.
- Ensure partial unionization at the pH of the oral cavity.
- The drug should have little sensitivity to environmental factors.
- It should be able to penetrate oral mucosal tissue.
- The therapeutic dose of the drugs should not exceed 40 mg [4].

IDEAL CHARACTERISTICS OF A DRUG AND FILM

- Thin, appealing film.
- Available in several sizes and forms.
- Not too noticeable.
- Excellent muco-adhesion.
- Rapid disintegration and dissolution.
- Quick release of drugs.
- Eliminates the first pass effect.

ADVANTAGES

- Convenient dosing.
- No water is needed.
- No risk of choking.
- Taste masking.
- Enhanced stability.
- Improved patient compliance.
- The drug enters systemic circulation with reduced hepatic first-pass effect.
- Site-specific and local action.
- The availability of a large surface area leads to rapid disintegration and dissolution within the oral cavity.
- Dose accuracy in comparison to syrup [5].

DISADVANTAGES

- Drugs that are unstable at the buccal pH cannot be given.
- Drugs that irritate the mucosa cannot be delivered via this method.

- Drugs with modest doses can only be administered.
- Taste masking is necessary for most medications due to their bitter taste.
- OFDFs require particular packing to prevent water damage due to their fragility.
- Dose homogeneity is a technical difficulty.
- Expensive packing for oral film [6].

Table 1. List of drugs that can be formulated as films.

Category	Examples
Anti-emetics	Ondansetron, granisetron, trimethobenzamide, dimenhydramine, metoclopramide, dolasetron
Serotonin inhibitors	Fluoxetine, setraline, paroxetine, fluxoamine, citalopram, alaproclate
5HT3 antagonists	Alosetron, ondansetron, palanosetron, rmosetron, alaproclate
Anti-epileptics	Carbamazepine, clonazepam, diazepam, divalproex sodium, fosphenyloin, phenytoin, primidone and valproate sodium
Anti-migraines	Almotriptan, dihydroergotamine mesylate, eletriptan, frovatriptan, sumatriptan and zolmitriptan
Dopamine D1 and D2 antagonists	A misulphide, bromperidol, cabergoline, domperidone, fenoldopam, metopimazine, pergolide mesylate, quetiapine, sulpiride
Nootropics	Almitrine dimesylate and raubasine, cevimeline hydrochloride, donepezil, galantamine, *Ginkgo biloba* extract (EGb 761), memantine, nicergoline
Statins	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, simvastatin

FORMULATION CONSIDERATIONS

Active Pharmaceutical Ingredient

ODFs can contain a variety of medications, including antihistamines, antidiarrheals, antidepressants, vasodilators, anti-asthmatics, and anti-emetics. Dimenhydrinate is another option to mask the flavor of ODFs. ODFs commonly contain salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, and other medications. Microcrystalline cellulose and additional film-forming polymers have also been used to create an ODF for an antiemetic medication, such as prochlorperazine.

Hydrophilic Polymers

Different polymers were used to alter the properties of the films. Premium-grade strips were made by mixing chitosan with either low- or high-methoxy pectin (HMP or LMP). Films made from cellulose-derived polymers such as methylcellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC) have lower water vapor barriers because of their hydrophilic nature. When combined with other polymers or used alone, polyethylene glycol (PEG) demonstrates good film-forming properties. HPMC is an excellent film-former, and many grades, such as Methocel E3, Methocel E5, and Methocel E15 Premium LV, are available. The development of a rapidly dissolving triclosan film manufactured using various grades of HPMC revealed that Methocel E15 Premium LV produced films of suitable quality. Fast-dissolving famotidine film produced using HPMC.

Plasticizers

Plasticizers generally enhance mechanical properties such as percent elongation and tensile strength in formulations. Typically, plasticizer concentrations range from 0 to 20% w/w. Among plasticizers are tributyl citrate, diethyl phthalate, triethyl citrate, PEG, and glycerol [7].

Saliva Stimulating Agent

The goal of these pharmaceuticals is to enhance saliva production, which aids the rapid dissolution of oral thin films. Saliva production is increased by the use of ionized acid, malic acid (citric acid), lactic acid (5-guar) powder, ascorbic acid, and tartaric acid. Two to six percent weight/weight units of these agents may be used either separately or in combination.

Flavoring Agent

Any US FDA-approved flavor can be used to hide the bitter taste of the formulation. These agents can be selected from synthetic or oleoresin. Extracts are obtained from various plant components, including leaves, fruits, and flowers. The quantity of added flavor depends on the specific type of flavor used. Essential oils such as menthol; robust mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, and clove; tangy fruit flavors such as lemon and orange; and sugary confectionery flavors such as vanilla and chocolate can all be incorporated. These flavors can be used alone or in combination to increase the complexity.

Sweetening Agents

Natural and synthetic sweeteners have been used to increase the palatability of mouth-dissolving formulations. Examples include saccharin and aspartame [8].

Surfactants

Surfactants are solubility enhancers that improve the wetting qualities of films, resulting in drug release and rapid dissolution. Various surfactants have been used. Examples include sodium lauryl sulfate, Tween, and benzalkonium chloride.

Colorants

Coloring agents were utilized to improve the visual appeal of the film. Pigments were used as coloring agents. Titanium dioxide is the most widely used colorant in ODFs and other pharmaceutical preparations. FD and C, custom Pantone-matched, and natural colors are among the many colors offered. The coloring agent concentration in rapidly dissolving films does not exceed 1% w/w [9].

METHODS OF PREPARATIONS OF FAST-DISSOLVING ORAL FILMS

Solvent Casting Method

The water-soluble polymers were dissolved to form a homogenous solution. Water-soluble substances such as drugs are dissolved in minimal water. The two solutions were combined by continuously swirling. Vacuuming eliminates the trapped air bubbles. The resulting solution was cast onto a petri dish and separated into fragments (Figure 1).

Semisolid Casting Method

This method is recommended for the preparation of films containing acid-insoluble polymers. Semisolid casting involves the use of heat-controlled drums to cast gel materials into films or ribbons. A gel mass was created by mixing an acid-insoluble polymer solution with a film-forming solution in sodium or ammonium hydroxide. When exposed to acids, cellulose acetate, butyrate, and phthalate are insoluble. The film-forming polymer and acid-insoluble polymer were mixed at a ratio of 1:4.

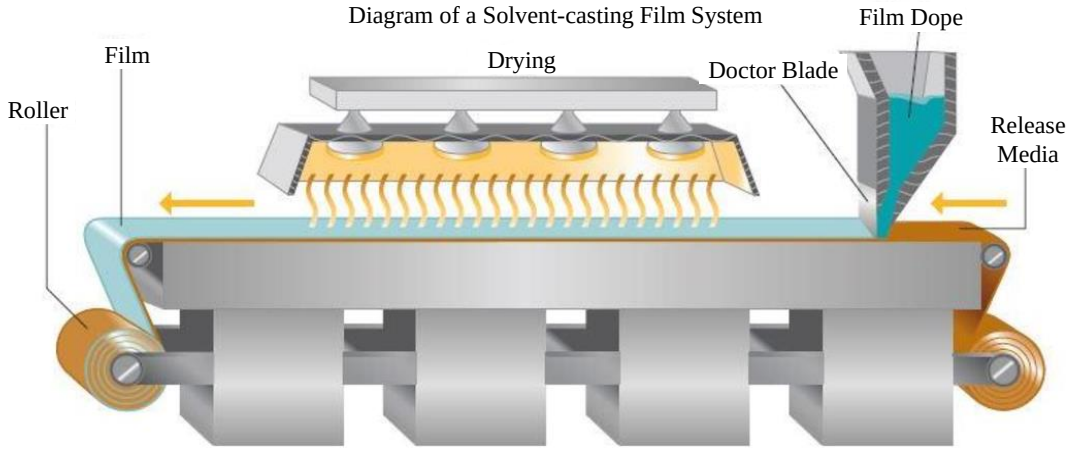

Figure 1. Solvent casting film system.

Hot-melt Extrusion Technique

Hot melt extrusion involves the combination of drugs and carriers in a solid form. The extruder was fed with dry granular material. Granules were processed for 3-4 minutes in an extruder barrel at a screw speed of 15 rpm. Zones 1–3 (zone-4) have recommended processing temperatures of 650°C, 800°C, 1150°C, and 1000°C. The extrudate was compacted into a cylindrical cylinder to form a film (Figure 2).

Solid Dispersion Method

This technique involves dispersing many drug candidates in a nonreactive carrier in a typical dosage form, together with amorphous hydrophilic polymers. The active ingredient in the medicine is dissolved in a suitable solvent to create a solution. A suitable polymer (PEG) was melted below 70°C and a solution was added without draining the liquid solvent. Solid dispersion was produced in films with dies.

Rolling Method

A medicine solution or suspension was prepared using a film-forming polymer and then run through a roller as a part of the rolling method. Suspensions are associated with certain rheological concerns. The solvent consisted primarily of water and an alcohol-water combination. After drying on the rollers, the film was cut into appropriate shapes and sizes [10] (Figure 3).

EVALUATION METHODS

Physical factors are crucial for ensuring uniformity across batches and for maintaining the aesthetic appeal of the final formulation. For surgical sutures and patches, the USP only requires a tensile strength test. Technical guidelines from other sectors of the economy, such as the plastics sector, can be used as models. Tensile testing for thin plastic sheeting can be performed using the ASTM International Test Method (D 882-02) or DIN EN ISO 527-1 and 527-3 rules [11].

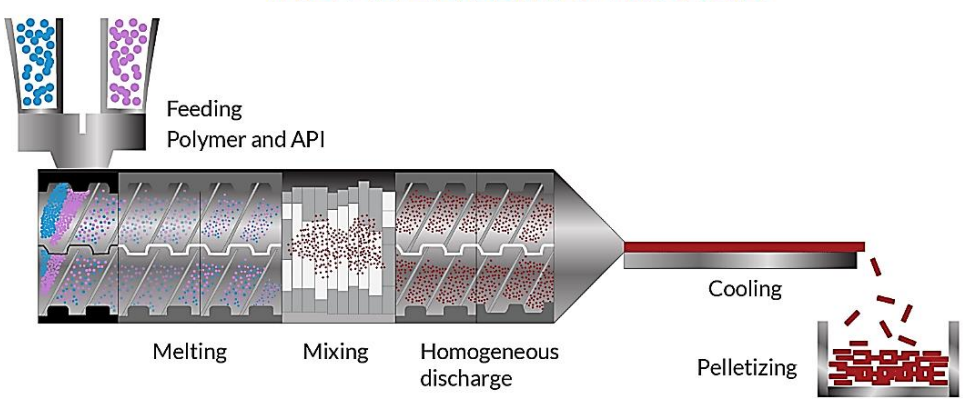

Figure 2. Hot melt extrusion process.

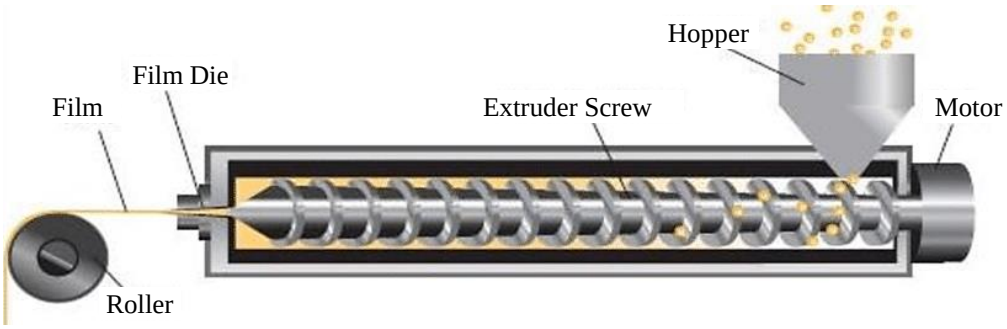

Figure 3. Rolling process.

Weight Uniformity

The films can be weighed on an analytical scale, and the average weight can be calculated for each film. This is useful for ensuring that a film includes an appropriate number of excipients and drugs.

Thickness

A micrometer screw gauge was used at five key locations on the film to measure its thickness. This is critical for determining the uniformity of the film thickness because it is directly related to the dosage accuracy.

Dryness Test

Film drying can be divided into eight stages: dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat, set-to-touch, dust-free, tack-free (surface dry), and dry-print-free. The term "tack" refers to how firmly a strip adheres to an object (a piece of paper) that has been pressed against it.

Surface pH

To conduct this test, the film was placed in a petri dish. After adding phosphate buffer (0.5 mL) to the sample, the sample was held for 30 s. The pH was measured by placing the pH meter electrode on the formulation's surface after a minute of acclimatization. The average of each formulation for the three determinations was calculated [12].

Tensile Strength

The highest tension at which a strip specimen breaks is referred to as the tensile strength. The following equation is used to calculate it by dividing the applied load at rupture by the cross-sectional area of the strip:

Tensile strength = Load at failure × 100/strip thickness × strip width.

Disintegration Time

The disintegration investigation involved randomly picking three ODF strips (2 cm × 2 cm) from each batch and placing them in a beaker containing 10 mL of pH 6.8 PBS. The time taken to dissolve the particles into smaller particles was monitored. The average time in seconds was analyzed in triplicate.

In Vitro Drug Release Studies

In vitro dissolution of MA from ODF strips was performed in a 50 mL beaker with 30 mL of pH 6.8 PBS at 37°C±0.5°C. Three ODF strips (2 cm × 2 cm) were randomly selected from each batch of the produced formulations and placed in three different beakers with PBS solution.5 ml The sample solution was withdrawn at 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300th sec and replaced with an equal volume of fresh medium. The beaker was shaken intermittently using a mechanical shaker. The absorbance of the withdrawn samples was measured using a UV-visible spectrophotometer at 285 nm [13].

APPLICATIONS

- Oral films are used to treat pain, sleep problems, allergies, and CNS diseases.
- Dissolvable films can be used for topical wound care including antibacterial and analgesic treatments.
- Dissolvable films can contain sensitive reagents for controlled release in biological fluids or can isolate several reagents for timed reactions with diagnostic devices.
- Oral films can improve the bioavailability of medications that are not easily absorbed [14].
- Dissolvable films comprise water-soluble and poorly soluble compounds with varying molecular weights, making them suitable dosage forms. The films may dissolve due to gastrointestinal enzyme secretion or pH, making them viable treatments for gastrointestinal problems.

- Dissolvable films can contain sensitive reagents for controlled release into biological fluids or serve as isolation barriers for timed reactions in diagnostic devices [15–18].

CONCLUSION

Most pharmaceutical companies operating in this sector are continuing their research and development efforts to modify their products for various categories to accommodate this technology, as OTFs have become a revolutionary trend. This technology is a novel medicine delivery device for all patient populations with swallowing issues, particularly juvenile and geriatric patients. OTFs are currently costlier to develop and manufacture than tablets. The thin film business is dominated by a few significant companies that have developed OTFs for certain medications, resulting in monopolization and consolidation. Tablets have a long history of well-established businesses. OTFs can provide an alternative to convenient dose forms. Extensive research is required for manufacturing and clinical testing. Although OTF technology has hurdles, optimizing research, formulation, and manufacturing shows great potential for the future. This rapidly disintegrating film drug delivery vehicle combines the benefits of solid and liquid dosage forms to create a stable and effective delivery method. However, this film dosage form faces challenges throughout formulation and development. Addressing these problems can aid future research and formulation as well as large-scale manufacturing.

FUTURE PROSPECTS

Oral films have promising potential, with continuous research aimed at improving and optimizing drug delivery methods. Personalized oral films have the potential to adjust medicine administration according to individual patient needs, making them a promising field of research. Personalized oral films can deliver medications at specific rates and locations, thereby enhancing patient outcomes. Another interesting research field is the application of nanotechnology in oral film formulations. Incorporating nanoparticles into oral film formulations improves the solubility and stability of the medication, leading to prolonged release. Smart oral films that respond to environmental stimuli, such as pH or temperature changes, are a growing research topic [19].

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