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Fast Dissolving Oral Films: A Comprehensive Review of Formulation Techniques and Therapeutic Potential

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ABSTRACT

Orally drug delivery film has received extensive interest duo to a distinct set of its advantageous properties compared to the traditional orally administered dosages, including faster rate of drug absorption, higher bioavailability and better patient compliance for children and elders with swallowing deficiencies. It increases the effectiveness of APIs by dissolving in the oral cavity in under a minute after coming into touch with less saliva than fast-dispersing tablets, without chewing, and without the requirement for water for administration. The fear of choking prevents many young and geriatric patients from taking these solid preparations. Consequently, orally dissolving pills have been developed. However, challenges in formulation, stability, and manufacturing exist, such as solubility issues and the selection of suitable drug characteristics. OFDFs are classified into flash release, mucoadhesive melt-away wafers, and mucoadhesive sustained-release wafers, each serving specific purposes. The composition of OFDFs involves water-soluble polymers, active pharmaceutical ingredients (APIs), plasticizers, and other excipients to ensure stability and efficacy. This review aims to summarize those newly developed oral films, discussing their formulation strategies, manufacturing methods as well as advantages and limitations thereof. Conclusions and future perspectives are also provided in brief.

Keywords: Fast Dissolving Oral Films, Formulation Techniques, Therapeutic Potential

INTRODUCTION

Oral route remains the most preferred drug administration route due to its simplicity and convenience with significantly improved patient compliance. However, the oral bioavailability of the drugs varies greatly, not only because the oral absorption is significantly impacted by their physicochemical properties and the physiological environment of the gastrointestinal (GI) tract, but also most of the drugs administered orally would suffer the first pass metabolism, In the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms formulate the fast dissolving tablets by using superdisintigrant/s and hydrophilic ingredients which has the higher bioavailability, quick action and most patient compliance. Many FDTs are prepared by using the expensive lyophillisation process and sometimes difficult to carry, store and handle (fragility and friability).also fear of chocking with fast dissolving tablet[1].

To eliminate the drawbacks of fast dissolving tablet a fast dissolving film can be placed. Fast dissolving films are very similar to ultra-thin strip. Innovative drug delivery forms called oral fast dissolving films (OFDFs) break down quickly within the mouth, making it easy to provide medication without the need for water or chewing . They offer numerous advantages, including enhanced bioavailability, precise dosing, improved patient compliance, versatility in drug formulation, discreet administration, suitability for diverse patient populations, stability, and portability. Oral fast dissolving films (OFDFs) have gained substantial significance in contemporary pharmaceutical research for several compelling reasons. OFDFs excel in enhancing patient compliance, particularly among populations such as children and the elderly, due to their user-friendly nature, rapid dissolution, and pleasant taste ,in contrast to conventional oral dose forms, this may lead to a quicker start of action and more effective drug delivery. Fast dissolving films are formulated using polymers, active pharmaceutical ingredients (API), plasticizers, saliva stimulating agents, sweeteners, flavors, preservatives and colors. Fast dissolving film is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by

saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed[2].

OFDFs open doors to personalized medicine approaches, enabling customized drug delivery based on individual patient preferences and needs. Their stability at room temperature and portability makes them adaptable for both clinical and non-clinical settings, including emergency situations, travel, and remote healthcare settings . Furthermore, OFDFs represent a dynamic field of research and development within the pharmaceutical industry their adaptability and benefits for the patient make them a viable platform for the creation of cutting-edge medication delivery systems.

Advantages of OFDFs over traditional dosage forms

1. Bioavailability: Oral fast-dissolving films offer improved drug bioavailability and site-specific targeting, leading to enhanced therapeutic efficacy.

2. Passive Drug Diffusion: These films utilize two penetration pathways: route paracellular and passive drug diffusion over the oral mucosa.

3. Patient Compliance and Convenience: As OFDFs are non-invasive and convenient to use, they are patient-friendly.

4. Non-Invasiveness: OFDFs are non-invasive, which makes them a preferred route over other oral dosage forms.

5. Site-Specific Drug Delivery: Drug delivery to certain locations in the mouth is possible with OFDFs, which improves the therapeutic effect of the medication.

6. Durable and Fragile: While traditional tablets and capsules are durable, OFDFs are fragile but still maintain their integrity until they reach the stomach.

7. Overcoming Resistance: OFDFs can be designed to release drugs at the back of the mouth, which can help in overcoming drug resistance.

8. Overcoming Physical Barriers: OFDFs can be designed to release drugs at the back of the mouth, which can help in overcoming physical barriers [3].

Challenges in formulation, stability, and manufacturing of OFDFs

1. Solubility: About 80% of new chemical entities (NCEs) in the pipeline face solubility challenges, leading to the production of poorly soluble OFDFs.

2. Nanosuspension: Because of the instability of nanosuspensions, it is difficult to formulate OFDFs loaded with them in order to increase the bioavailability of paroxetine.

3. Nanoemulsion: The development of fast-dissolving nano-emulsion-based sublingual films is hampered by the instability of nano-emulsions.

4. Nano-emulsion-in-oil: The replacement of microplastics in capsules with oil- dispersions is a challenge due to the instability of oil dispersions.

5. Fast-dissolving films loaded with microplastics: The replacement of microplastics in capsules with oil-dispersions is a challenge due to the instability of oil-dispersions.

6. Fast-dissolving films loaded with active ingredients: Challenges include maintaining the stability of the active ingredients in the film and overcoming the limitations of oil dispersions.

7. Fast-dissolving films loaded with polymers: Challenges include maintaining the stability of the polymers in the film and overcoming the limitations of oil dispersions [4].

Special features of Fast Dissolving Films

• Thin elegant film

• Available in various size and shapes

• Unconstructive

• Fast disintegration

• Rapid release

• Have an acceptable taste.

• Give a pleasing mouth feel.

• Should not leave residue in mouth[5].

Tablet 1: Composition of Film Active Pharmaceutical agents[8]

Sr. No	Category	Percentage amount%
1	Drug (API)	1-30%
2	Polymer	40-50%
3	Plasticizer	0-20%
4	Surfactant(Solubility Enhancer)	q.s
5	Saliva stimulating agent	2-6%
6	Sweetening agent	3-6%
7	Flavoring agent	0-10%
8	Coloring agent	q.s
9	Stabilizing agent or Thickening agent	0-5%

Composition of OFDFs:

The composition of OFDFs is carefully formulated to achieve these characteristics while ensuring the stability and efficacy of the active pharmaceutical ingredients (APIs). Typically, OFDFs consist of the following essential elements.

1.Polymer Matrix: The primary structural component of OFDFs is a water-soluble or water-dispersible polymer matrix, which forms the film's backbone. Common polymers used include hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), polyvinyl alcohol (PVA), and pullulan. The necessary characteristics of the film, such as mechanical strength, disintegration rate, and API compatibility, dictate the choice of polymer.

2. Active Pharmaceutical Ingredient (API): The API is the therapeutic agent intended to provide the desired pharmacological effect. It is incorporated into the OFDF formulation in a finely dispersed or molecularly dispersed form, ensuring uniform distribution within the film matrix.

3.Plasticizers: To increase the film's elasticity and flexibility, plasticizers are added to the mixture, making it more comfortable for patients to handle and ensuring proper film formation. Common plasticizers include polyethylene glycol (PEG), glycerine, and sorbitol.

4.Sweeteners and Flavouring agent: To improve the palatability and patient acceptance of OFDFs, sweeteners (e.g., sucralose, mannitol) and flavouring agent (e.g., mint, fruit flavours) may be included. These additives mask the taste of the API and provide a pleasant sensory experience during administration.

5.**Disintegrants:** Disintegrants are used to facilitate the rapid disintegration of the film upon contact with saliva. Common disintegrants in OFDFs include crospovidone and croscarmellose sodium. **Surfactants:** In order to facilitate the film's wetting and quick disintegration in the oral cavity, surfactants could be added. They increase the API's bioavailability. Common surfactants include polysorbates and sodium lauryl sulphate.

6.**Antioxidants and Preservatives:** These additives are used to protect the stability of the API and prevent degradation due to exposure to light, oxygen, or moisture.

7.Colorants: Colorants are optional and are added for aesthetic purposes, allowing for differentiation between different OFDF formulations[6].

Methods of manufacture of fast dissolving films

One (or a combination) of the following processes may be used to manufacture the oral films:

• Solvent casting

• Hot-melt extrusion

• Semisolid casting

• Solid dispersion extrusion

• Rolling.

1. Solvent Casting Method:

For the production of OFDFs, this is one of the most used methods. To create a homogenous solution, the active pharmaceutical ingredients (APIs) and a suitable solvent is used to dissolve the film forming polymers. After that, a thin layer of the solution is dried and cast onto a level surface [7].

• Steps:

1.Selection of film-forming polymers and plasticizers.

2.Dissolving the polymer, plasticizer, and API in a volatile solvent (e.g., ethanol).

3.Casting the solution onto a flat surface (e.g., glass) using a casting machine or a spreader. 4.Drying the cast film to remove the solvent, leaving behind a thin, flexible film (Figure 1). 5.Cutting the film into the desired dosage forms.

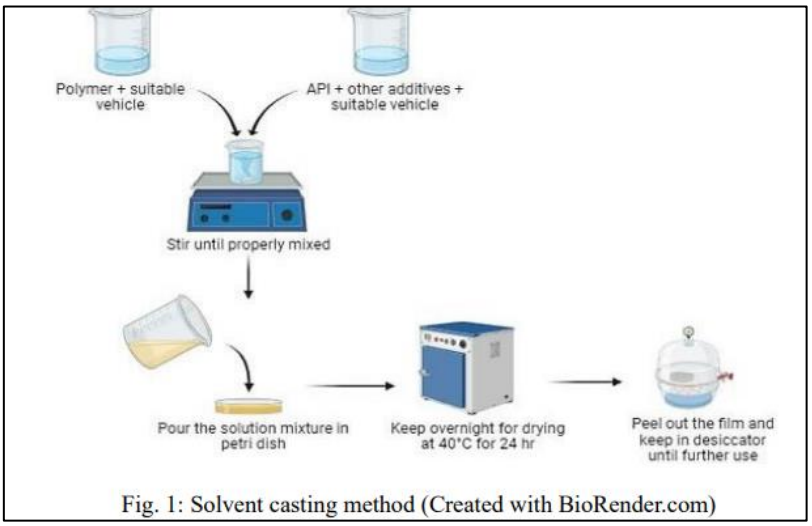

Fig. 1: Solvent casting method (Created with BioRender.com)

2.Hot Melt Extrusion method (HME):

In HME, the polymer is melted, the API is added, and the mixture is then extruded through a die to create a film. This is a continuous production procedure [8].

Steps:

1. Melting the polymer and plasticizer.

2.Mixing the API into the molten polymer.

3. Creating a thin film by extruding the mixture through a die.

4. Cooling and solidifying the film.

5. Cutting the film into the desired shape and size (Figure 2).

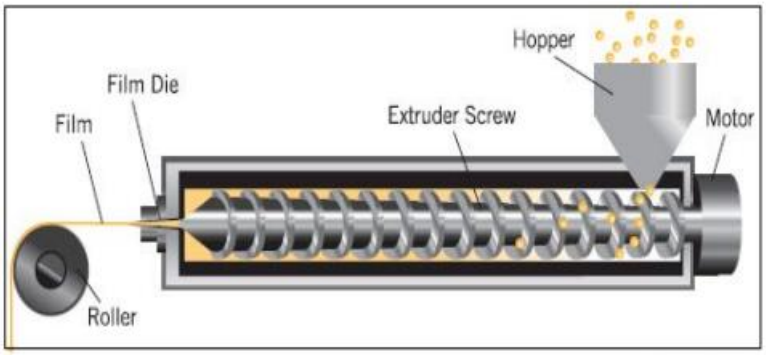

Figure2: Hot melt extrusion

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3.Semisolid casting[9]

Solution of water soluble film forming polymer is prepared. Resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate). Appropriate amount of plasticizer is added so that gels mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

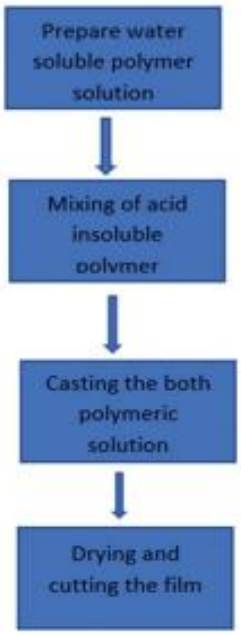

Figure 3- semi solid casting

4.Solid dispersion extrusion

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Drug is dissolved in a suitable liquid solvent. Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70 ◦ C Finally the solid dispersions are shaped into the films by means of dies.

5.**Rolling Method**

This method involves rolling out a mixture of polymer, plasticizer, and API between two rollers to form a thin film (Figure 4) [10].

• Steps:

1. Mixing the polymer, plasticizer, and API to form a uniform dough-like mass.

2. Feeding the dough between two closely spaced rollers.

3. Adjusting the gap between the rollers to achieve the desired film thickness.

4. Cutting the film into individual doses.

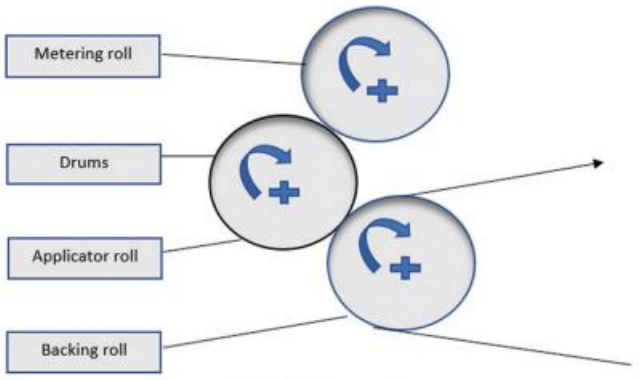

Fig. 4: Rolling method

Characterization of fast dissolving films[11].

Drug-excipients interaction studies Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (X-RD) can be used to assess possible drug excipient interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalipies of the reaction.

Thickness

Thickness test can be carried out using an electronic micrometer. The thickness of the film sample should be measured at five locations (center and four corners), and the mean thickness is calculated. Samples with air bubbles, nicks or tears and having mean thickness variation of greater than 5% are excluded from analysis.

Folding endurance

To determine folding endurance, a strip of film is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Swelling index

The studies for swelling index of the film are conducted in stimulated salivary fluid. The film sample is weighed and placed in a pre weighed stainless steel wire sieve. The mesh containing the film is submerged into 50 ml of stimulated salivary medium contained in a mortar. Increase in weight of the film is determined at each interval until a constant weight is observed. The degree of swelling is calculated using the formula:

$$SI = wt – wo /wo$$

Where SI is the swelling index,

wt is the weight of the film at time “t”,

wo is the weight of film at t = 0

Tensile strength

The tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film. Evaluated this mechanical property by using Testing Instrument. Film strips in special dimension and free from air bubbles or physical

imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Tensile strength is also defined as the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross- sectional area of fractured film from the following equation.

Tensile strength (N/mm 2) = breaking force (N) /cross sectional area of sample (mm 2)

Percent elongation:

The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation can be obtained by following equation:

% Elongation =Increase in length at breaking point(mm)×100 /original length(mm)

Palatability test:

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade it would be the very good formulation. Grades: A= very good, B= good, C=poor.

Disintegration test:

Disintegrating time is defined as the time (second) at which a film breaks when brought into the contact with water or saliva. The disintegration time is the time when a film starts to break or disintegrate. Thickness and mass play a role in determining the dissolvable films physical properties. Disintegration test is done by Disintegration apparatus.

Dissolution test:

Dissolution is defined as the amount of drug substance that goes into the solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent concentration. In vitro release studies are carried out in modified USP XXIII apparatus (paddle over disk).

Stability study:

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance.

FTIR

Studying compatibility using FT-IR spectroscopy, IR grade KBr was separately mixed with pure drug and drug coupled with polymers, then transformed into KBr pellets by a hydraulic press and scanned across a range of 4000–400 cm-1 [12].

XRD

To ascertain the crystallinity of raw medications and drugs included in films, X-ray diffraction was used. For the purpose of analyzing the amorphous/crystalline behavior of treated medicines, diffraction patterns were acquired [13].

Studies on differential scanning calorimetry (DSC)

To ascertain potential interactions between the medication and excipients, DSC experiments were carried out using a Perkin-Elmer DSC-4 system, calibrated using an indium standard [14].

Drug release kinetics

The release data were fitted to the following kinetic models to study the mechanism of drug release. Kinetics of zero order Qt = Q0 + k0t

Where Q0 is the starting dose of the medication in the pharmaceutical dosage form, Qt is the dose at time t, and k0 is a zero-order rate constant.

Initial-order kinetics ln Qt = lnQ0 + k1t or Qt = Q0 e-k1t

Where Q0 is the initial concentration of the drug in the solution, Qt is the amount of drug released at time t, and k1 is the first-order release constant. Dissolution efficiency (DE) was proposed by Khan as a useful metric for the assessment of in vitro dissolution data [15].

Oral Fast Dissolving film packaging

In the pharmaceutical industry, the packaging must preserve the product's efficacy and stability to ensure its therapeutic integrity. Safeguarding the dose of other rapidly dissolving dosage forms during production and storage necessitates costly packaging, particular processing, and extra caution. For fast-dissolving films, there are several packaging choices. Films are medicinal items that must be packaged in singles; the most popular package type is an aluminium bag. The Rapid card is a unique and exclusive packaging solution created by APR-Labtec that is specifically made for the Rapid films. Three raid videos are stored on each side of the credit card-sized quick card. Each dosage can be removed on its own. The chosen material must possess distinct properties as outlined in our thorough investigation [16].

➢ Packaging materials must provide barrier protection against external environmental factors to preserve the integrity of the product inside.

➢ In accordance with regulatory requirements set forth by the Food and Drug Administration (FDA), packaging materials utilized in the food industry must obtain approval for their safety and suitability.

➢ Packaging materials should conform to established tamper-evident standards in accordance with relevant regulatory requirements.

➢ To ensure safe packaging, materials must adhere to stringent safety standards and be deemed harmless by rigorous scientific evaluation.

➢ The selected packaging materials should not elicit any adverse chemical or physical interactions with the product during storage or transportation.

➢ Packaging materials should not impart flavors or odors to the product to maintain its sensory integrity.

Blister Packs:

Blister packs are a popular choice for packaging OFDFs. Each OFDF unit is placed in an individual blister cavity, which provides protection against environmental factors, ensures dosing accuracy, and facilitates easy removal of each unit. Blister packs are also tamper-evident.

Aluminium Foil Pouches:

Aluminium foil pouches provide excellent moisture and light barrier properties. The OFDF units are sealed within the pouch, protecting them from external factors. These pouches are often used for larger quantities of OFDF units [17].

Application of fast dissolving film18

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of FDFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders. Dissolvable FDFs evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products.

Topical applications:

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

Gastro retentive dosage systems:

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and could potentially be used to treat gastrointestinal disorders.

Diagnostic devices:

Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

Conclusion

Oral fast-dissolving films (OFDFs) have revolutionized pharmaceutical research and drug delivery. They offer rapid dissolution, enhanced patient compliance, and versatility in delivering medications, making them a compelling alternative to conventional dosage forms. Despite formulation and manufacturing challenges, OFDFs have gained a foothold in the market, driven by patient preferences for convenience and specialized drug delivery. The future holds promising innovations, including nanotechnology and 3D printing, which will further expand their potential. Overall, OFDFs represent a commitment to improving medication delivery, catering to diverse patient needs, and advancing pharmaceutical science, promising a brighter future for both healthcare providers and patients.

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