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The Use of Oral Fast Dissolving Films: An Approach to Treat Oral Candidiasis

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ABSTRACT
Medicine is a science of unpredictability and the art of possibility. The advancements in drug delivery hold the promise to minimize dose-dependent side effects and increase biological activity while facilitating patient adherence. Oral films are the focus of attention these days as a substitute approach to the conventional dosage form. The oral films are most convenient to swallow for geriatric and pediatric patients, having dose accuracy with rapid release of the drug, used for systemic and local action which makes it an excellent system of drug delivery. The major cause of oral candidiasis (also known as oral thrush) is Candida albicans in people who take immunosuppressive drugs and those with a previous history of hyposalivation, prolong use of an antibiotic drug, diabetes mellitus, and have poor oral hygiene. In recent days, Oral Fast Dissolving Films (OFDFs) of some prominent antifungal drugs such as Fluconazole, Miconazole, Itraconazole, Nystatin, and Clotrimazole are in huge demand because of their high permeability in oral mucosa which increases the bioavailability of the drug. Oral film demand is expected to be worth 15.984 million US$ at the end of the financial year 2024. Since, the discovery and development of a new API molecule are a difficult, expensive, and time-consuming process so, the pharmaceutical companies have turned on their focus in developing new dosage forms from existing drug molecules. The present review mainly provides an account of salient features of OFDFs, various formulation considerations, method of preparation, evaluation of OFDFs along with highlights of market potential. Additionally, it also discusses the work done on oral films of antifungal drugs (Antifungal drugs used to treat oral candidiasis) and the use of herbal drugs in oral films to treat oral candidiasis as a future consideration.
KEYWORDS: Oral Films, Oral Fast Dissolving Films, Candidiasis, Bioavailability, Drugs.

I. INTRODUCTION

Oral candidiasis (OC) is a commonly encountered oral disease that is caused due to overgrowth of Candida species, especially by Candida albicans. In general,theCandida species lives in a symbiotic relationship with healthy humans and causes no harm, but affects patients that are having a depressed immune system which may result in local and systemic infections [3]. The most common causative agent of oral candidiasis is C. albicans, although other species of candida also remain active, namely- C. glabrata,C. tropicalis and C. parapsilosis[4].

In past years, it has been estimated that the occurrence of fungal infections has increased and is more prevalent in developed countries. There are certain predisposing and risk factors associated with OC including immunosuppression (due to HIV and chemotherapy), systemic diseases (like Diabetes), alteration in oral flora (caused by prolonged use of antibiotics), corticosteroid therapy, hyposalivation (as a result of local and systemic disorders, medications or chemotherapy), poor buccal hygiene and ill-fitted dentures.

OC can be treated by both local as well as systematic treatment using various antifungal agents. Long-term use of antifungal agents systemically, to treat the OC, produces possible adverse effects. Therefore, to minimize the adverse effects, local therapy by antifungal agents is considered the first-line treatment for OC. Even so, it is difficult to achieve by conventional formulations such as oral gels, creams, pastes, lotions, solutions, suspensions, mouthwashes, lozenges, mouth paints, and so on. This is because of lack of retention time, inaccurate dosing, and low volume for dissolution which further results in inconstancy or changeability, or instability in the salivary drug concentration. These problems also lead to noncompliance or no acceptance among patients and show variability in therapeutic performance.

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Gel preparations are used topically and applied right to the concerned area in the oral cavity to circumvent the systemic action seen after gastrointestinal absorption. But after application, it becomes tedious for old patients to spread the gel uniformly in the oral cavity with the help of their tongue [3].

A limited count of drugs is available for the treatment of OC. Nystatin and Amphotericin B are the two most common antifungal agents used locally. Some azoles like Ketoconazole, Miconazole, Voriconazole, andEchinocandins are also used for the treatment of OC, but produce systemic side effects and cause interaction with other drugs [4]. Therefore, a huge call or invocation to work upon novel antifungals, for efficacious drug delivery. As it is known that the process of discovery and development of a new drug will demand a very long time with huge expenses, so pharmaceutical companies turned on their focus in developing new dosage forms for existing drug molecules.

Oral Fast Dissolving Film (OFDF) is one such relatively new dosage form.Due to ease of intake, pain reduction, flexibility (to accommodate different kinds of drug candidates), and most notably, patient compliance, oral administration is the most common path. Moreover, solid oral delivery systems do not require sterile conditions and are thus less costly to produce. This delivery system is very well recognized amongst pediatrics and geriatrics.

OFDFs are the solid dosage form that melts rapidly when placed in the mouth without the intake of water or chewing. This system is a replacement for tablets, capsules, and syrups, which circumvent the issue of swallowing [9]. The ideology behind the evolution of oral films is transdermal patches [6].

As time passed, drug administration through the buccal route came into significance and even the utilization of polymeric films has also been developed for the buccal route, which can also be named as oral fast dissolving films (OFDFs). These films give action against local disease (for example, OC) on the mucosa. From the literature view, it is seen that permeability of oral mucosa is roughly 4-4,000 times more than the skin but less as compared to the intestine. Buccal delivery thus acts as an ideal medium for the ingestion of molecules with low dermal penetration and for those drugs, which are more susceptible to gastrointestinal degradation [7].

The perfect fast-dissolving delivery system should possess the following characteristics:
Ease to handle and apply, no extra processing or packaging, maximum stability, shippable, don't require water for administration and give an agreeable taste. Hence, they provide compliance among elderly and child patients; bedridden patients; or in case of those suffering from dysphagia, vomiting, Parkinson's disease, mucositis, sudden allergic reactions, or coughing (due to an active daily life) [7,8]. Besides, they are helpful when local treatment is needed like local anesthesia for toothaches, cold sores (caused by Herpes simplex virus), or teething [7].

Pfizer, a global pharmaceutical corporation formulated Listerine® pocket packs™, which was the first type of oral strip (OS) for the freshness of the mouth. Also, a medicinal oral film (OF) was developed for the cure of sore throat, constituted with 7- benzocaine named Chloraseptic® relief strips [8].

Oral fast-dissolving film preparation includes constituents such as active pharmaceutical ingredients (API), saliva stimulating agents, film-forming polymers, plasticizers, coloring agents, sweetening agents, flavoring agents, cooling agents, thickening and stabilizing agents, surfactants, and permeation enhancers [8].

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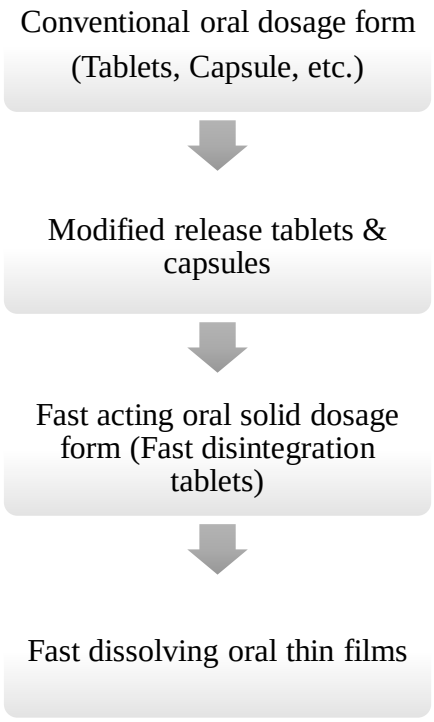

Figure 1:Stages in the Development of Oral Solid Dosage Forms

1.1 Oral Fast Dissolving Films (OFDFs)

- Oral films (OFs) also referred to as oral wafers are used as an effective pharmaceutical dosage form in mouth/oral care.
- Oral films, a novel dosage form proved to be a solution for the drawbacks of liquid state dosage form and combined the benefits of the solid dosage form with it.
- OFs are of the size of a postage stamp and prepared using a very simple and common method called the solvent casting method. This process involves, solubilizing film-making agents in a solvent system and casting the resulting solution into a film by pouring it on a uniform or even surface. Upon evaporation of the solvent, the remaining film is cut into desired pieces and further processed for packaging.
- Oral films are formulated using water-soluble polymer (Hydrophilic polymers) rupture or disintegrate quickly when comes in contact with the saliva and deliver active medicine to the affected area of the mouth cavity or into the systemic circulation through the oral mucosa.
- The rate of the total amount of saliva secreted from the minor and major salivary glands under typical physiological conditions of mouth is 1-2 ml/min.
- A fact is that oral films do not require any extra efforts to popularize the way of administration of this dosage form, because, OST-derived films were alreadyfamiliarized in the market (e.g.- breath-freshening strips) among people in the initial of the 2000 year [9].

1.2 Salient Features of Fast-Dissolving Drug Delivery System

- Simple administration for patients with mental disabilities.
- Water is not necessary for administration.
- Provide taste masking, hence circumventing the poor taste of drugs.
- Can be formulated to leave a negligible amount of residue in the oral cavity and give freshness to the mouth.
- Capacity to offer liquid drug benefits in the form of solid preparation.
- Adjustable and acceptable to modern manufacturing and packaging.
- Economical.

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1.3 Advantages

- Quick disintegration of oral fast dissolving films (OFDFs) circumvents the first-pass metabolism and gives immediate onset of action, for example- in cases of pain.
- OFDFs overcome the difficulty of swallowing, hence enhancing compliance among geriatric and pediatric populations.
- Permeability of oral mucosa is greater, thus increasing the systemic availability of the drug.
- Since no amount of water is needed for administration, thus OFDFs provide ease for traveling patients.
- The oral cavity provides a large surface area, therefore, the drug breakdown and dissolves at high speed.
- Better uniformity of film thickness and high flexibility make it easy to handle, store and transport.
- A variety of shapes and sizes of films are available in the market.
- This dosage form serves enhanced efficacy, taste masking and provides no risk of choking.
- Since the drug directly goes into blood circulation, due to which OFDFs produce the fastest onset of action.
- OFDFs also provide site-directed and local action.

1.4 Disadvantages

- A high quantity of API cannot be incorporated into OFDFs (It must be around 1-30mg).
- The substance which remains unstable at pH of mucosa and irritates the mucosa layer is not suitable for administration through this dosage system.
- The cost required in packaging would be high because of the weak structure of this dosage form.
- Specific packaging machinery is needed.
- Acquiring the uniformity of dose is a tough task in this.
- To cast the oral films Petri dish cannot be used.
- It can absorb moisture in a humid environment.
- The solubility of the polymer in water and the volatile solvent is necessarily required.

1.5 Criteria for Choosing Drug Candidate

- The substance to be incorporated in the oral films must have a pleasant taste.
- A high amountof drugs is not required.
- It should be able to permeate through mucosal tissues of the oral cavity.
- Drug solubility and drug stability in water and saliva should be good.
- Drug candidates of less and moderate molecular weights should be chosen.
- Partly unionized drugs at oral pH must be selected.

II. ANATOMY AND PHYSIOLOGY OF ORAL MUCOSA

The outermost layer of oral mucosa consists of stratified squamous epithelium, below which a basement membrane is located, followed by lamina propria, and the innermost layer called sub-mucosa lies (As shown in Figure 2). The buccal mucosal site possesses a stable and smooth surface with vascular perfusion, while the sublingual region of mucosa does not have a stationary surface. If seen in comparison to other mucosal sites of the oral cavity, the buccal mucosa is more resistant to potent allergens, with the least effect and it also lowers the enzymatic activity. The drug assimilation/absorption occurs in two ways i.e., either transcellular (passing from one cell to another, through the adjacent cell membrane) or paracellular route (across the intercellular spaces between the cells). In terms of permeability, oral/buccal mucosa is in-between as compared to the epidermis (skin) and intestinal mucosa. Thus, the wafer disintegrates and dissolves quickly in the oral cavity, and absorption of the active molecules occurs directly in the systemic circulation [6].

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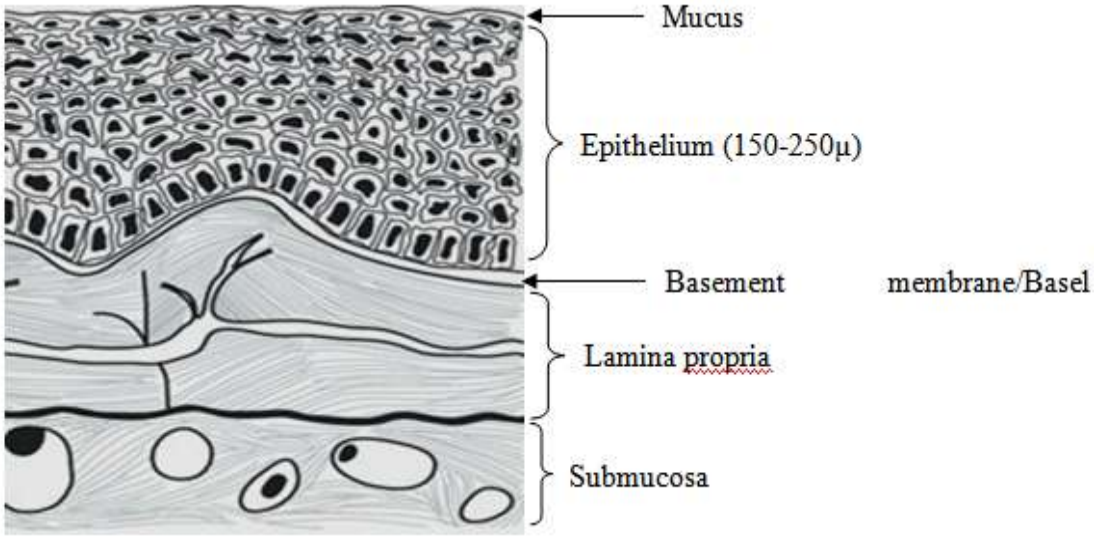

Figure 2:Different Layers of Oral Mucosa

III. MECHANISM OF DRUG DELIVERY FROM OFDFS

Oral fast-dissolving films are thin and flexible films for oral drug delivery. Drug-loaded oral films are taken orally and can be made to rapidly disintegrate when placed on the tongue.
The oral films dissolve in seconds when coming in contact with saliva, releasing the drug which has been dissolved within the matrix without the requirement of additional water. The drug reaches directly into the bloodstream through the oral mucosa. Thus, prevents the first pass effect resulting in rapid onset of action.

IV. FORMULATION CONSIDERATION

4.1API-

It is possible to deliver several APIs through oral fast dissolving films. There is a difficulty while incorporating high-dose drugs because they require a high dissolution time. On the other hand, small-dose drugs are the best candidates to be incorporated into oral films. A typical composition for oral fast dissolving films is 5%w/w – 30%w/w of APIs. Mostly, APIs in the micronized form are preferred to be incorporated into films to improve the texture and dissolution property of films that will lead to the immediate action of the drug. Most of the APIs have a bitter taste. So, to minimize the bitter taste, various taste-masking agents can be used.
The ideal properties of an API are-

- The drug must have a low dose of up to 40mg.
- The drug must be highly lipophilic.
- The drug must be less bitter and more potent.
- The drug must be soluble in water and saliva.
- The drug must have good permeability through the oral mucosa.
- The drug must be partially unionized in oral mucosa pH.

The antifungal drugs which are effective against Candida albicans and ultimately can be used for the treatment of oral candidiasis - Itraconazole,Fluconazole, Clotrimazole, Miconazole & Nystatin [75].

4.2 Polymers-

Polymer is one of the main ingredients used in the development of oral fast dissolving films, as the film formation and its mechanical strength depend on the appropriate choice and concentration of the polymer. Mainly, the water-soluble polymers are utilized alone or in the combination with other polymers. Typically, about 60-65%w/w of the concentration of water-soluble polymer is preferred to attain the desired property of the film. Various natural and synthetic polymers are used for the preparation of oral film which plays an important role in the delivery of the drug by dissolving rapidly in the oral mucosa when it comes in contact with the saliva of the mouth. [TABLE 1]

The ideal properties of the polymer are-

- The polymer must be non-toxic and should not cause any secondary infections in the oral mucosa.
- The polymer must be bitter less and tasteless.

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- The wetting and spreading properties of the polymer should be good.
- The polymer must have a good shelf life.
- The polymer must have a good penetration-enhancing property.
- The polymer must be water-soluble, have low molecular weight, and should have an excellent film-forming capacity.
- The polymer must exhibit sufficient mechanical and tensile strength.
- The polymer must be readily available and inexpensive.

4.3 Plasticizers-

The plasticizer is a key component in the formulation of oral fast dissolving films. The selection of plasticizers depends on their compatibility with the polymer and the form of solvent used in the film casting. It helps to improve the mechanical property like tensile strength and flexibility of the film and lowers the brittleness of the film. It provides better film properties by decreasing the glass transition temperature of the polymer to 40-60°C for the non-aqueous solvent system and the aqueous system below 75°C. Generally, the concentration of plasticizers used is 0-20 % w/w of the dry polymer weight. [TABLE 1]

The ideal properties of plasticizers are-

- Plasticizers must be compatible with the drug and other excipients used in the film formulation.
- Plasticizers should not cause any interaction with the polymer.
- Plasticizers must be volatile.
- Plasticizers should enhance the strength and flexibility of the film by reducing the glass transition temperature of the polymer.

4.4 Saliva Stimulating Agents-

Saliva stimulating agents are used to increase the secretion of saliva which aims for rapid disintegration and dissolution of the film in the oral mucosa. They may be used alone or in combination and the concentration of saliva stimulation agents should be between 2-6% w/w of the weight of the film. Generally, the acids used in food processing may be used as salivary stimulants but a few sweeteners may also use sometimes them as salivary stimulants. [TABLE 1]

4.5 Sweetening Agents-

Sweetening agents have become the most essential part of masking the bitter taste of drugs in oral films. The concentration of sweeteners used in the formulation of the film is 3-6% w/w. To improve the palatability of oral fast dissolving films, natural as well as artificial sweeteners are used. [TABLE 1]

4.6 Flavoring Agents-

Flavoring agents are added in the oral film formulation to impart the flavor and provide some zest to the formulation. The flavors may be selected depending on the taste and ethnicity of an individual. Depending on the preference of individuals from various age groups, any US-FDA-approved flavor may be added to the formulation. Flavors used in the preparation of the films must be compatible with the drug and other excipients. Generally, up to 10%, w/w flavors are preferred to be added in the oral film formulation. [TABLE 1]

4.7 Coloring Agents-

These are the agents used to provide color to the formulation and make it eye-pleasing. Pigments like titanium dioxide and FDC-approved natural coloring agents are generally used which should not exceed the limit of concentration 1% w/w. [TABLE 1]

4.8 Cooling Agents-

Cooling agents are added in the formulation of oral films to increase the flavor and provide freshness to the oral cavity. WS23, WS3, and Utracoll II are some cooling agents that are used with a mixture of flavors. [TABLE 1]

4.9 Surfactants-

Surfactants are added in the preparation of oral films which may act as solubilizing, wetting, and dispersing agents used to dissolve the film within seconds and release the drug immediately. They are also utilized to enhance the solubility of poorly soluble drugs. [TABLE 1]

4.10Stabilizing & Thickening Agents-

The stabilizing and thickening agents are used to enhance the dispersion or solution viscosity and consistency of the strip preparation solution or suspension before casting. Natural polymers can be used as a thickening and stabilizing agentin concentration up to 5% w/w. To enhance the film characteristics, other ingredients such as surfactants

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and emulsifying agents are also added in limited quantities. [TABLE 1]

Table 1: List of Various Excipients Used in Formulation of OFDFs

EXCIPIENTS	CATEGORY	EXAMPLES
Polymers	Natural Polymer	Gelatin, Pullulan, Pectin, Sodium Alginate, Malto Dextrin
	Synthetic Polymer	Carboxymethylcellulose, Hydroxypropyl methylcellulose, Polyvinyl alcohol, Sodium carboxymethylcellulose, Hydroxypropyl cellulose.
Plasticizers	Citrate Derivatives	Tributyl Citrate, Triethyl Citrate, Acetyl Citrate, and Castor Oil
	Phthalate Derivatives	Diethyl Phthalate, Dimethyl Phthalate, Dibutyl Phthalate
	Others	Glycerol, Propylene glycol, Polyethylene glycol
Saliva stimulating agents	Acids	Citric acid, Malic acid, Ascorbic acid, Tartaric acid and Lactic acid
	Sweeteners	Glucose, Fructose, Maltose, Xylose and Lactose
Sweetening agent	Artificial	First Generation:Saccharin, Cyclamate, Aspartate Second Generation: Suralose, Acesulfane-k, Alitame, Neotame
	Natural	Sucrose, Dextrose, Glucose, Fructose, Maltose.
Flavoring Agents	Fruit	Cherry, Apple, Pineapple, Strawberry
	Salt	Butterscotch, Apricot, Mint, Peach
	Oils	Cinnamon Oil, Peppermint Oil, Spearmint oil
	Sweet	Vanilla, Berry
	Sour	Citreous flavor, Raspberry
	Bitter	Chocolate, Wild cherry, Walnut
Coloring Agents	--	Titanium dioxide, FDA Approved coloring agents
Cooling Agents	--	WS23, WS3 and Utracoll II
Surfactants	--	Sodium lauryl sulfate, Benzalkonium chloride, tweens, spans, and poloxamer407
Stabilizing & Thickening Agents	--	Xanthan gum, Carrageenan, Locust bean gum, and Cellulosic derivatives

V. METHOD OF PREPARATION

5.1 Solvent Casting Method-

In this method, the water-soluble polymer is dissolved in distilled water along with the plasticizer and saliva stimulating agent, and this solution is then continuously stirred in a magnetic stirrer at 60°C and 1000rpm for up to 4 hours. After that, the solution is placed for 1 hour to remove any trapped air bubbles from it. At the same time, the API is dissolved in distilled water along with other excipients like sweetening agent, flavoring agent, etc. for 45 minutes with continuous stirring. Now, in a separate beaker, both the solutions are mixed and stirred up to 1 hour and 1000rpm with the help of a magnetic stirrer at room temperature. At 60°C, the prepared solution is then cast and dried. Finally, cut into the films of the desired size. The films prepared by this method are uniform and flexible.

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5.2 Semi-Solid Casting Method-

Firstly, a water-soluble polymer solution is prepared. Then, the resulting solution is transferred to the solution of an acid-insoluble polymer (e.g.- Butyrate cellulose acetate and Phthalate cellulose acetate) that can be prepared with sodium hydroxide and ammonium hydroxide. A specific amount of plasticizer is added to obtain a gel mass. Lastly, with the help of a heat regulating drum, the gel obtained is cast into the film. The film thickness should be approximately 0.015-0.05 inches. There must be a ratio of 1:4 between the acid-insoluble polymer and film-forming polymer.

5.3 Hot-melt Extrusion Method-

In this method, a hot-melt extruder is used. Firstly, the drug and polymer are mixed for 10 minutes in a mixer and slowly the plasticizer is added to it. The mixer is granulated in the presence of an anti-sticking agent. The prepared granules are dried at room temperature overnight and the dried granules are sieved in a 250µm sieve. These granules are processed inside the drum for less than 3 minutes approximately keeping the speed of the extruder to around 15rpm.

The processing temperature must be-

- Zone 1 – 80°C
- Zone 2 – 115°C
- Zone 3 – 100°C
- Zone 4 – 65°C

At temperature 65°C, the extrudate is then pressed into a cylinder calendar to obtain a film of thickness of 200µm approximately. The film is then cut into the desired shape and size and stored at a temperature of 25°C. Low molecular weight and viscosity polymers are used, without any use of organic solvent and water. This method is employed for poorly soluble drugs.

5.4 Solid Dispersion Extrusion-

In this process, the drug is dissolved in an appropriate liquid solvent. The resultant solution is added to the melted polymer solution which may be achieved below 70°C without removing the liquid solvent to form a solid dispersion. Eventually, with the use of dyes, the resulting solid dispersions are turned into films.

5.5 Rolling Method-

In this method, the solution of the drug is prepared in a solvent containing water or a combination of alcohol and water. The resulted drug solution is mixed with the film-forming polymer completely. Then the prepared solution or suspension of specific rheological property is subjected to the roller. The film is dried on the rollers and cut into a suitable shape and size.

VI. EVALUATION

6.1 Drug Excipients Interaction Studies-

During solid dosage form development, assessment of incompatibilities between different excipients & API plays an important role in formulation stages. The possible drug excipients interaction can be assessed by using Fourier Transformer Infrared Spectrum (FTIR) and Differential Scanning Calorimeter (DSC). [24]

6.2 Thickness-

An electronic micrometer or calibrated digital Vernier Caliper can be used for measuring the thickness of the film. [25] To ensure the uniformity of film thickness, the film is measured at the center and four corners & the mean thickness of the film is calculated. The film has a mean thickness variation of more than 5% are excluded, films with tears, bubbles, or nicks are also excluded.

6.3 Percentage Elongation-

Percentage elongation is a way to quantify & measure the flexibility of film percentage elongation calculated by determining how much distance traveled by a pointer before the film break. It is measured by a machine known as,'Hounsfield Universal Testing Machine'.

$$\text{Percentage elongation} = \frac{(\text{finallength} - \text{initiallength}) \times 100}{\text{initiallength}}$$

The percentage elongation of the film is increased by increasing the concentration of the plasticizer.

6.4 Dryness/Tack Test-

Dryness test of the film is done to check, dry to recoat, dust-free, dry to handle, dry to print, tack-free, dry to touch, dryness of film measured by pressing a piece of paper (an accessory) on the film & checking adherence of paper on film.

6.5 Tensile Strength-

Tensile strength is the point at which the strip is broken on applying strength. Tensile strength is calculated by the stress applied to break upon the cross-section area of the film.

$$\text{Tensile strength} = \frac{\text{maximumstrengthappliedtobreak}}{\text{thicknessoffilm} \times \text{filmwidth}}$$

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6.6 Moisture Content-

The moisture content of the film affects the brittleness & friability film. Moisture content is determined by the weighing method or Karl Fischer titration. Typically, the pre-weighted film is heated to 100-120°C until constant weight gain is attained. The difference of final weight & initial weight gives the amount of moisture content present in the film [45].

$$\% \text{ Moisture Content} = \frac{\text{initialweight} - \text{finalweight}}{\text{initialweight}} \times 100$$

6.7 Young's Modulus-

Young's modulus is used to measure the stiffness of the film, calculated by the ratio of stress applied over the stain in the region of elastic deformation [46].

$$\text{Young's Module} = \frac{\text{slope}}{\text{filmthickness} \times \text{cross headspeed}} \times 100$$

6.8 Swelling Properties-

The swelling property or the swelling index of the film is determined by placing the film in a stimulated saliva solution. The pre-weighted film sample is placed in the stainless-steel wire mesh. Then the mesh is submerged into a container with a 15 ml medium in it.

$$\text{Swelling index} = \frac{wt - w0}{w0}$$

Where, wt. = weight of film at time t.
w0 = weight of film at time zero.

6.9 Tear Resistance-

Tear resistance/tear strength is a measure of how much the film resists the effect of tearing. Tear resistance was recorded by applying load at a rate of 51 mm/min & recorded near the onset of tearing. Unit of tear resistance is Newton's or pound-force [67].

6.10Surface pH-

The surface pH of the film is used to determine the side effect of the film in vivo. The film is placed on the surface of 1.5 %w/v agar gel & the pH is determined (usually pH paper used).

6.11 pH of the Film-

the pH of the film is determined by using a Ph meter or pH paper by dissolving the film in 2ml distilled water[68].

6.12 Folding Endurance-

Folding endurance is the number of times the film folded at the same place without breaking the film[68].

6.13 Transparency-

The transparency test is determined by using a rectangular shape film placed into the internal side of the UV spectroscopy cell and examined under 600 nm transmittance.

It is calculated by the formula,

$$\text{Transparency} = \frac{(\log T600)}{b} = -€c$$

Where, b = thickness of the film in nm.
c = concentration.
T600 = transmittance at 600nm.

6.14 Organoleptic Evaluation-

Oral fast-dissolving films are made to disintegrate rapidly in the oral cavity, the film needs to have organoleptic palatable property which is acceptable to a large mass of thepopulation.Sweetness & flavor evaluation done by special controlled human taste panels. Taste assessment apparatus is used for an In-vitro study [69].

6.15 Assay/Content Uniformity-

Content uniformity is determined by the assay methods given for particular API in Pharmacopoeias. 85-115% is the limit for content uniformity.

6.16 Disintegrating Time-

Disintegrating time is the time required to break the film after getting in contact with saliva. 30 seconds or less time is required for the disintegration of film as per CDER.

There are two different methods for evaluating the in-vitro disintegration time of the film.

i. Petri plate method-
2ml of distilled water is added to the Petri plate & the film is dipped. The time required to completely dissolve the film is measured.

ii. Slide frame method-
One drop of distilled water is pipette out & drop into the film, after that the film is placed planner & clamp to Petri plate. The disintegration time required to dissolve film completely or make a hole in it is recorded.

VII. MARKET POTENTIAL OF OFDFS

An oral fast dissolving film is the fast and emerging advanced drug delivery over traditional oral method, because of easy to administer & low-

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cost manufacturing, and increased patient compliance. Now day's oral films are trending in the pharmacy field due to their less fragile nature as compared to other oral dose forms, rapid release, dose accuracy, ease of administration. Oral films have 2-3-year shelf life depending upon the API but are usually sensitive to moisture present in the environment[7,70].

As per the 2015-2025 market potential for OST, owns a good growth perspective for upcoming technology.Some oral films are in the market and many are in the stage of various preclinical & clinical trials. Technology like rapid film, pharma film, Bio-FX, etc. covers up to 38% market. Thus, it is a potential field for research and the oral film demand is expected to be worth 15.9843 million US$ at the end of the financial year 2024. The estimate of mixed annual performance in the worldwide market is a 9.0% growth rate (CAGR) with a significant increase of compound annual growth rate (CAGR) of 18.3% between 2016-2024. North America has a leading market share of 85.3%.

Gas X & Listerine breath freshener are some trending OTC drugs, suboxone film has obtained market acceptance in a short duration of time, other products like Breakyl, Zuplenz & Onsolis are also progressing in many topographies. NUTherapeutics & Avishkar Pvt. Ltd. in Hyderabad, while ZYM Laboratories established in Nagpur are some new companies in India, established their business in a very short period. Monool Rx, Lts Lonmann & Warmer Lambert established their market in India & have filed their patents in the Indian patent office (IPO). The key players in the oral film technology market are Applied pharma research, Monosol Rx, Novartis AG, Pfizer, Wolfers K Luwer, Allergen & Solvay[71,72].

VIII. DISCUSSION

8.1Production of Itraconazole Nanocrystal-Based Polymeric Film Formulations for Immediate Drug Release-

For the treatment of oral candidiasis, The Itraconazole Nanocrystal-Based Polymeric Film Formulations for Immediate Drug Release was prepared from the film casting method using hydroxypropyl methylcellulose (HPMC) as a film-forming polymer and glycerine as a plasticizer which showed immediate release behavior and improved solubility. The disintegration time of these films was found below 3 min. The film formulations showed a good appearance, favorable dispersibility of the drug nanocrystals from the films, high homogeneity of films, adequate physical characteristics like smooth surface structure with good flexibility, favorable disintegration time, and immediate drug release profiles [74].

8.2 Formulation and Evaluation of Fluconazole Loaded Oral Strips for Local Treatment of Oral Candidiasis-

Fluconazole loaded buccal Mucoadhesive oral strip for local treatment of oral candidiasis was formulated by solvent casting method. Oral strips were found to be smooth and elegant in appearance, uniform in thickness, weight, and drug content. The disintegration time was found 23–28 s. The rate of release of fluconazole from oral strips was ≈96%. The optimum formulation was stable for 6 months. The in-vitro antifungal activity studies proved the efficacy of the oral strip for a longer period against Candida albicans [2].

8.3 Preparation and Evaluation of Mucoadhesive Buccal Films of Clotrimazole for Oral Candida Infections-

Mucoadhesive buccal films of clotrimazole for local delivery of the drug to the oral cavity were prepared by the solvent casting method using polypropylene glycol as the plasticizer. The in-vitro adhesion time of the film was found 4 hours and maintained the concentration of clotrimazole in the dissolution medium (isotonic phosphate buffer pH 6.6) above the MIC of Candida albicans for about 4 hours. A maximum concentration of 21.1µg/ml was obtained in the dissolution medium after 2 hours. The drug released from the formulation was found to be microbiologically active [83].

8.4 In vitro Evaluation of Miconazole Mucoadhesive Buccal Films-

Film dosage forms containing miconazole for the treatment of oral candidiasis were prepared using water-soluble polysaccharides. To treat oral candidiasis, miconazole is administered in the oral cavity to act directly at the affected site. Probably, miconazole dissolves immediately upon contact with saliva, secreted at 1.5 - 2.0 ml/min from the salivary glands following stimulation. Miconazole incorporated into such film dosage forms can dissolve into a small amount of saliva as soon as the form disintegrates. Therefore, film dosage forms modified with a surfactant are useful for treating localized problems in the oral cavity, such as oral candidiasis [82].

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IX. FUTURE PERSPECTIVE OF OFDFS

As an alternative approach to the conventional dosage form, oral fast dissolving films are gaining a lot of popularity and expanding steadily because of their several advantages over conventional dosage forms.

Currently, there is huge interest in traditional or 'green medicine' which is safe and more effective than expensive synthetic medicines. Additionally, there are several side effects of synthetic antifungal drugs such as headache, dizziness, abdominal pain, nausea, vomiting, pruritus, hypokalaemia, itching, muscle pain, skin rash, etc., and also the microbial resistance is produced by long term use of these antibiotics. Therefore, there is an increasing requirement for alternative treatment and prevention methods that could be efficient, safe, and feasible.

The reliability and use of herbal drugs are of growing concern over the past two decades because of the side effects and risk factors of synthetic drugs. Hence, for future consideration, the OFDFs of herbal drugs could be formulated for the treatment of oral candidiasis caused by Candida albicans.

Herbal drugs such as neem (Azadirachta indica), clove (Syzygium aromaticum), and amla (Emblica officinalis) are studied to be effective against Candida albicans in various research studies [76,77].

In the research study of 'Bansal et al, the extract of neem and clove was found to have an antifungal effect against Candida albicans [76] The study showed that the minimum inhibitory concentration of neem and clove was found to be 5.0 mg/ml and 5.5 mg/ml for Candida albicans.

'Potdar et al' in their research study found the minimum inhibitory concentration of ethanolic and acetonic extracts of amla at 0.09% against Candida albicans[77].

Hence, from the various research studies, it can be concluded that neem, clove, and amla are the most effective and potent herbal drugs against Candida albicans which is a major cause of oral candidiasis.

Therefore, the herbal drugs can prove to be an efficient way in future consideration to treat oral candidiasis by formulating the OFDFs of neem, clove, and amla having less or no side effects as compared to the synthetic antifungal drugs.

X. CONCLUSION

It can be concluded from the above that; the oral fast dissolving films have proved to be a novel approach as compared to the conventional dosage form in terms of both therapeutic efficacy and patient compliance. Due to the fast disintegration of oral films in oral mucosa, the drug incorporated in it can produce quick action. OFDFs have also proved to be an innovative method to treat oral candidiasis by formulating oral films of various antifungal agents effective against Candida albicans, the major cause of oral candidiasis. Oral film technology is expanding rapidly which has become a great concern of challenge among the pharmaceutical companies to develop oral fast dissolving films for a wide range of APIs. The above study also explores the possibilities of incorporating various herbal drugs in OFDFs for the treatment of oral candidiasis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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