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REVIEW ARTICLE

FAST DISSOLVING ORAL FILM: A REVIEW

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ABSTRACT:
In the late Nineteen century, rapidly disintegrating drug delivery systems were developed as an alternative to capsules, tablets, and syrups for geriatric and pediatric patients with dysphagia. To meet these needs, many orally disintegrating tablets have been commercialized that disintegrate in the mouth within a minute without chewing or drinking water. Oral drug delivery technology has since been upgraded from conventional dosage forms to modified-release dosage forms, and more recently, rapidly disintegrating films have been developed instead of orally disintegrating tablets. Orally dissolving fast-dissolving films (OFDFs) have recently entered the market because they are more convenient and easier to use compared to other dosage forms such as orally disintegrating tablets. The technology has evolved in recent years from the confectionery and oral care market in the form of breath strips to become a novel form that is widely accepted by consumers, attracting many pharmaceutical industries interest in his OFDF. A rapidly dissolving film in the mouth is a type of drug delivery system that disintegrates or dissolves within seconds without absorbing water when placed in the oral cavity. OFDF is very similar in shape, size, and thickness to a postage stamp. These films have the ability to deliver drugs systemically via intragastric, sublingual, or buccal routes of administration and are also used for topical effect. This type of technology provides a convenient way to administer medications to the general population as well as special populations such as children, the elderly, bedridden patients, and psychiatric patients. Some companies have introduced a more robust form of fast-dissolving drug delivery that places a film on or under the tongue. When this film is applied to the tongue, it immediately dissolves and releases the drug, which dissolves in saliva. Some drugs are absorbed through the mouth, throat, and esophagus when saliva enters the stomach. In such cases, the bioavailability of the drug is improved, the risk of choking is eliminated, and the mouthfeel is improved. The current review describes various formulation considerations, manufacturing processes, and quality control of OFDF.

Keywords: Fast (Quick) dissolving Oral films, Oral strips, Tensile strength, Immediate Release.

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INTRODUCTION:

Rapidly dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms. These systems consist of solid dosage forms that rapidly disintegrate and dissolve in the oral cavity without water [1]. Fast-dissolving drug delivery systems include orally disintegrating tablets (ODT) and oral thin films (OTF). The Center for Drug Evaluation and Research (CDER) defines ODT as "a solid dosage form containing a drug that dissolves rapidly when placed on the tongue, usually within seconds" [2]. The USFDA defines an OTF as "a thin,

flexible, non-friable polymeric film strip containing one or more dispersed active pharmaceutical ingredients, placed on the tongue for delivery in the gastrointestinal tract into saliva before swallowing." It is intended to dissolve or dissolve quickly." [3]. OTFs are becoming more and more mainstream medicines. The first prescription OTF approved was Zprenz (ondansetron hydrochloride – 4mg, 8mg) in 2010. A second approval followed shortly after Suboxone (buprenorphine and naloxone). Statistics show that 4 out of 5 of his patients prefer orally disintegrating dosage forms to conventional solid oral administration. These factors, combined with convenience and compliance benefits, have (and will continue to) pave the way for the growth of ODT and OTF drugs. This review focuses on different types of polymers, different types of manufacturing techniques, and evaluation tests for oral films [4].

Ideal properties of a fast-dissolving oral film:

1. Thin elegant film
2. Available in various sizes and shapes
3. Discreet [5]
4. Excellent adhesion to mucous membranes
5. Five. rapid disintegration and dissolution
6. Rapid drug release
7. Bypass the fast pass effect [6]

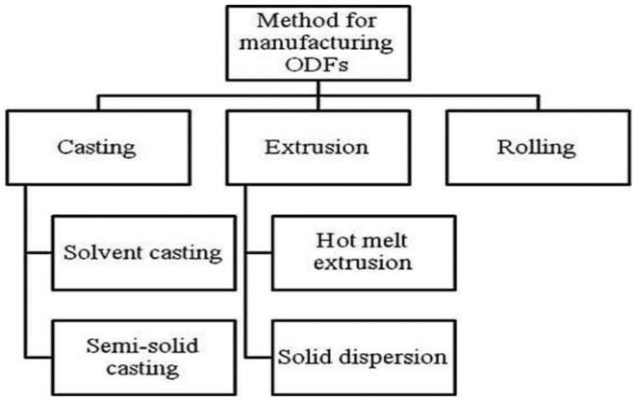
Advantage of orally fast dissolving oral films:

1. No water is required for dosing.
2. Useful for pediatric, elderly, and aphasic patients with dysphagia.
3. Due to the large surface area of the film, it degrades and dissolves rapidly in the oral cavity [7].
4. By bypassing the hepatic first-pass effect, it increases bioavailability and acts quickly.
5. Reduced dosage, reduced side effects and improved efficacy and safety profile [8].
6. Flexible and portable for easy handling, transportation and storage.
7. Ease of administration to psychiatric, disabled, uncooperative patients, and patients with reduced fluid intake or nausea [9].
8. Effective for motion sickness, acute pain, sudden allergic attacks, asthma attacks, coughs, etc. where ultra-quick action is required.
9. Stability over time as drug remains in solid dosage form until consumed.
10. Dosing accuracy compared to liquid formulations.
11. It has a pleasant mouth feel and leaves little or no residue in the mouth after administration [10].

Disadvantages of FDOF:

1. Dose uniformity is difficult to maintain.
2. Only those active pharmaceutical ingredients having small dose can be incorporated [11].
3. Require expensive packaging.
4. Since OTFs dissolve quickly, dose termination is impossible.
5. OTFs are not official in any pharmacopoeia [12].

Figure 1: Manufacturing methods of FDOF:



Manufacturing methods of FDOF:

1. Solvent casting
2. Semisolid casting
3. Hot melt extrusion Method
4. Solid dispersion extrusion
5. Rolling

1. Solvent Casting:

Dissolving the water-soluble components to form a clear viscous solution, dissolving the drug along with other excipients in a suitable solvent, then mixing and stirring both solutions, and finally using the solvent casting method.

Therefore, it is preferable to formulate a rapidly dissolving buccal film. The cast was placed in a Petri dish and allowed to dry [13].

Figure 2: Flow chart of Solvent Casting method

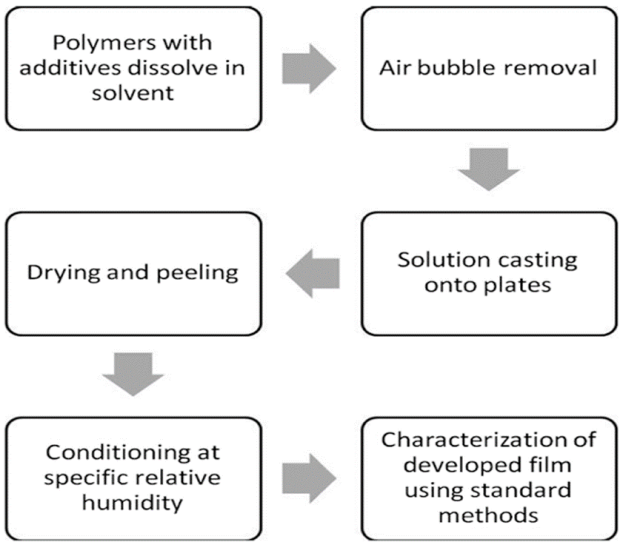
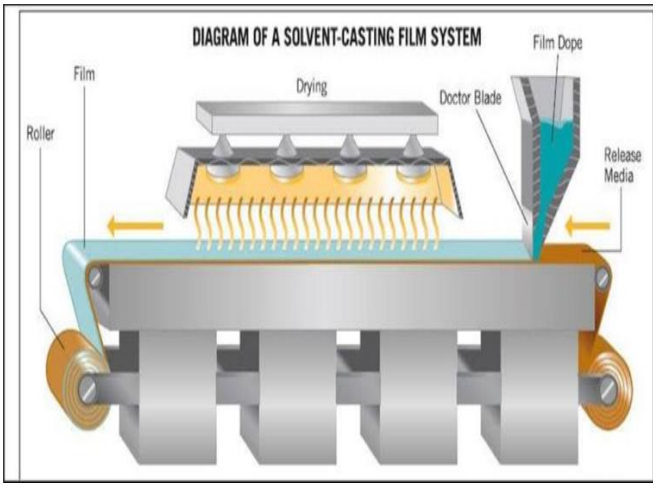


Figure 3: Solvent Casting method



2. Hot Melt Extrusion:

Hot metal extrusion is commonly used to manufacture granules, sustained release tablets, transdermal and transmucosal drug delivery systems. Melt extrusion was used as a manufacturing tool in the pharmaceutical industry in 1971 [14]. In the hot melt extrusion process, the drug is first mixed with solid excipients. An extruder with a heating element then melts the mixture. Finally, the melt is formed into a foil through a nozzle. The hot melt extrusion process has several advantages.

- Reduction in operating units
- Improved content consistency
- Waterless process.

Figure 4: Flow chart of Hot Melt Extrusion

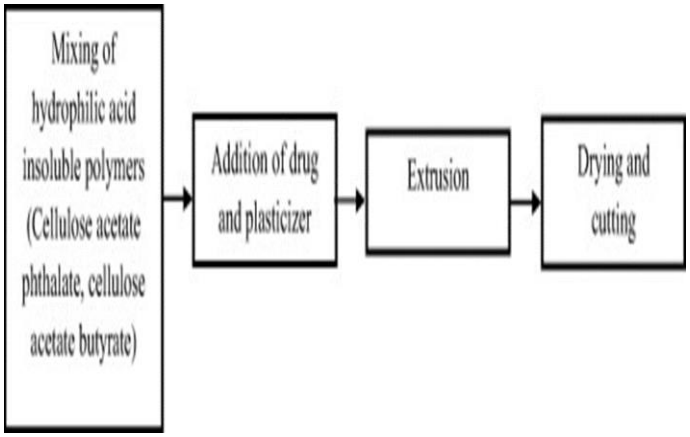
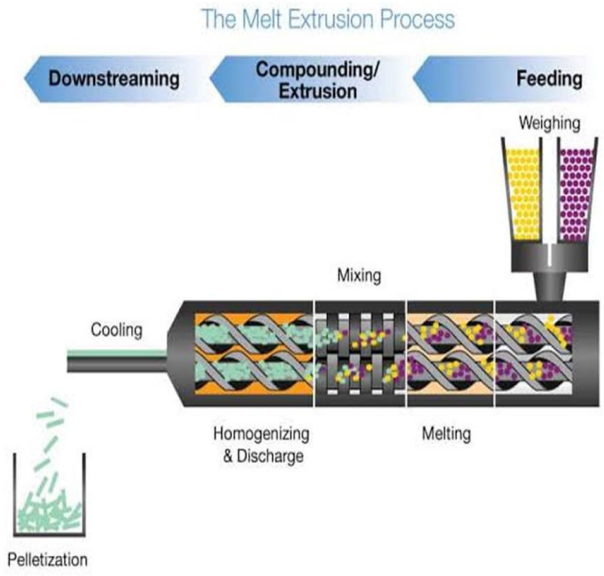


Figure 5: The melt Extrusion Process



3. Semisolid Casting:

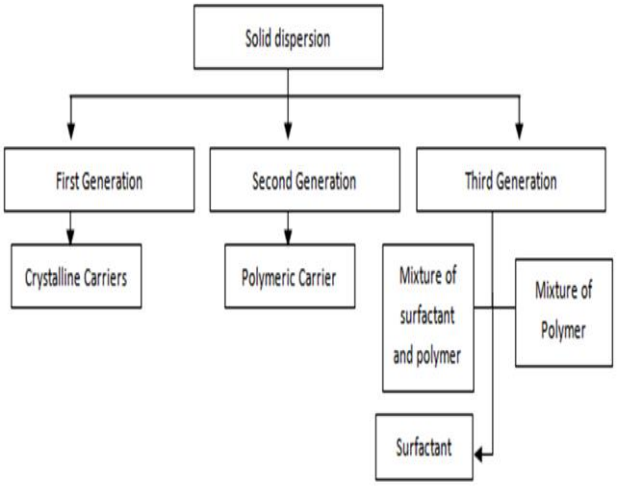
A solution of a water-soluble film-forming polymer is prepared. The resulting solution is added to a solution of acid-insoluble polymer (eg, cellulose acetate phthalate, cellulose acetate butyrate). Appropriate amount of plasticizer is added to obtain a gel mass. Finally, a heat-controlled drum is used to cast the gel mass into a film or tape. The film thickness should be approximately 0.015 to 0.05 inches. The ratio of acid-insoluble

polymer to film-forming polymer should be 1:4 [15].

4. Solid Dispersion Extrusion:

The term solid dispersion refers to a dispersion of one or more active ingredients in an inert carrier in solid state in the presence of an amorphous hydrophilic polymer. The drug is dissolved in a suitable liquid solvent. The solution is then incorporated into a polyethylene glycol melt available below 70°C. Finally, a mold is used to shape the solid dispersion into a film.

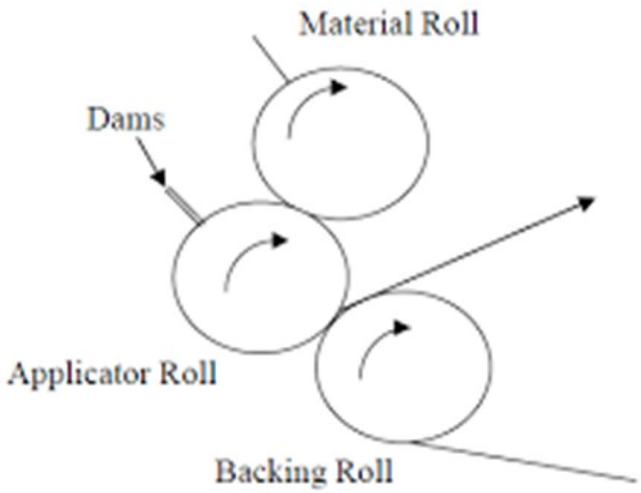
Figure 6: Flow chart of Solid Dispersion Extrusion



5. Rolling Method:

In this method, the film is prepared by preparing a masterbatch, adding the active ingredient, and then forming the film. Prepare a premix containing film-forming polymer, polar solvent, and other additives except drug. Add the premix to the masterbatch feed tank. It was fed to either the first or second mixer, or both, via a first metering pump and control valve. Add the required amount of drug to the desired mixer. Mix the drug with the masterbatch premix to obtain a homogeneous matrix. A constant amount of homogeneous matrix is then fed into the ladle by a second metering pump. The film is finally formed on the substrate and discharged onto the backup roll. The wet film is then dried by controlled soil drying [16].

Figure 7: Rolling Method



patented technologies of FDOF:

1) XGel:

XGel is the core of Meldex International's intellectual property and is used in all foil systems and ingestible delivery techniques. Developed by BioProgress, his XGel sheet technology is revolutionizing the products and manufacturing methods currently available in the pharmaceutical industry. X gel film may improve product stability. It was also developed for non-ingestible applications such as cosmetics, ostomy bags, sanitary and healthcare products. A process called “solution casting” is used to develop and manufacture XGel films [17].

2) Soluleaves:

With this technology, the film is made to release the active ingredient upon contact with saliva. This applies to aroma-releasing products such as mouth fresheners, confectionery and vitamin products. SOLULEAVES technology enables efficient delivery of active ingredients into the oral cavity in a comfortable, portable form. This delivery system can be used in the therapeutic areas of cough/cold, gastrointestinal and pain treatment, and nutritional supplements. SOLULEAVES films can also be designed to adhere to mucous membranes and slowly release active ingredients over 15 minutes [17].

3) Wafertab:

WAFERTAB is a drug delivery system that encapsulates an active pharmaceutical ingredient in an ingestible film. It is a patented delivery system that uses a unique process to produce a drug-laden thin film that can be used for topical or oral application. Active ingredients are incorporated into the film after casting. The WAFERTAB system offers many opportunities for innovative drug design by connecting multiple films with different active ingredients [17].

4) Foamburst:

FOAMBURST is a foam film capsule patent issued in September 2004. Gas is blown into the film during manufacturing to create a honeycomb film. The voids in the film can be gas-filled, voided, or filled with other materials to create specific flavor-blasting properties or release active ingredients. Due to the light honeycomb structure, the capsules melt quickly, providing a melt-in-your-mouth sensation. FOAMBURST has attracted confectionery manufacturers as a means of delivering and releasing flavours[17].

5) Micap:

Micap entered into an option agreement in 2004 to combine its expertise in microencapsulation technology with Bio Progress's water-soluble films. This development aims to provide a new delivery mechanism for the $1.4 billion global market for quit-smoking products (SCPs) [17].

Evaluation tests for FDOF:

Thickness:

As the thickness of film is directly concern with drug content uniformity so it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers at different strategic locations [18].

Dryness test/tack tests:

Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.

Tensile strength:

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\textit{Tensile Strenght} = \frac{\textit{Load at failure} * 100}{\textit{Strip thickness} * \textit{Strip width}}$$

Percent elongation:

When stress is applied, a strip sample stretches, and this is referred to as strain. Strain s basically the deformation of strip divided by original dimension of the sample. Generally, elongation of strip increases as the plasticizer content increases [19].

$$\% \textit{ Elongation} = \frac{\textit{Increase in length} * 100}{\textit{Original Length}}$$

Young's modulus:

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\textit{Young modulus} = \textit{Force at c.strain} \div \textit{Cross sectional area} \times 1 \div \textit{Corrosponding strain}$$

Where,

C= Corresponding

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation [20].

Tear resistance:

The tear strength of a plastic film or sheet is a complex function of its ultimate tear strength. Basically, a very low load rate of 51 mm (2 in)/min is used, designed to measure the force that initiates tearing. The maximum stress or force required to rupture the sample (usually found near the onset of rupture) is recorded as the burst strength value in Newtons (or pounds-force).

Weight Variation:
Weight variation is studied by individually weighing 10 randomly selected films and by calculating the average weight.

Folding endurance:
Fold durability is determined by repeatedly folding the strip in the same place until it breaks. The number of folds without breaking is calculated as the folding endurance value.

Surface pH of film:
To investigate possible side effects in vivo, the surface pH of the rapidly dissolving films was determined. Since acidic or alkaline pH can cause irritation of the oral mucosa, it was decided to bring the surface pH as close to neutral as possible.A combined pH electrode was used for this purpose. pH was measured by contacting an electrode to the surface of a pre-wetted oral film [21].

Swelling property:
Film source studies are conducted using a simulated saliva solution. Weigh each film sample, place it on a pre-weighed stainless steel wire mesh screen, and immerse it in 15 mL of media in a plastic container. Film weight gain was measured at preset time intervals until a constant weight was observed. Calculate swelling degree using parameters.

$$\alpha = (Weight - Wo) / Wo$$

Wt is the weight of the film at time t and wo is the weight of the film at time 0.

Transparency:
Film transparency can be determined using a simple UV spectrophotometer. Cut the film sample into a rectangle and place it inside the spectrophotometer cell. Measure the transmittance of the film at 600 nm. Film transparency is calculated as:

$$Transparency = (logT600)/b = - €c$$

Where, T600 - the transmittance at 600 nm
and b is the film thickness (mm) and
c - concentration.

Assay/ Content uniformity:
This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115%[22].

Disintegration time:
Disintegration of films that dissolve rapidly in the mouth requires a US disintegrator. The disintegration time limit of 30 seconds or less for orally dissolving tablets as stated in the Center for Drug Evaluation and Research (CDER) guidelines can be applied to fast dissolving oral strips. Disintegration times vary by formulation, but typically the disintegration range is 5-30 seconds. However, there is no official guidance for orally rapidly disintegrating filmstrips [23].

Dissolution test:
Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

Stability studies:
Stability studies have to be carried out at accelerated condition (65% relative humidity and 35 ºC temperature) in the humidity chamber [24].

Table 1: Marketed preparation of fast dissolving oral films:

Sr.	Drug Name	Active Ingredient	Category	Indication	Mfg.by
1	Eclipsed flash strips	Mint	Antibacterial	Mouth freshener	Wringleys
2	Health Strips	Soluble vitamins	Soluble Vitamins	As A Supplement	Mattle/ Momentus solution , LLC
3	Benadryl	Diphenhydramine hydrochloride	Antihistamin, allergy, sinus	Treatment of cough	Pfizer
4	Tetraflu thin strips [25]	Dextromethophan	Antitusive	Cough	Novartis
5	Oral films	Benzocain	Local Anesthetic	Sore Throat	Apothecus Pharmaceutica Corporation
6	Sudafed PE	Phenylephrine	Decongestant	Nasal and sinus congestion	Pfizer
7	Orajel	Menthol/pectin	Local Anesthetic	Canker sores,fever blisters	Del
8	Zentrip	Medizine Hydrochloride	Antihistamic	Nausea, vomiting with motion sickness	Sato
9	Melatonin PM	Melatonin	Sedative, hypnotics	Insomnia	AdvaCare
10	Bioevelop	Nicotin			Paladine Labs Inc.
11	Listerin Pocketpaks	Mint	Antibacterial	Mouth freshener	Pfizer inc
12	Azatidine Maleate[26]	Azatidine	Antihistaminic	Perennial and allergic rhinitis	Fulford (India) Ltd
13	Habitrol	Nicotine	Smoking cessation	To reduce smoking habit	Dr.Reddy's laboratories

14	Loperamide	Loparamide Hydrochloride	Anti- diarrheal	Diarrhea	Ralington Pharma LLP(India)
15	Zofran ODT[27]	Ondansetron	Anti emetic	Prevent nausea and vomiting	Dr.Reddy's Laboratories
16	Covan[28]	Triplodine hydrochloride	Antihistaminic	Relieve sneezing & runny nose	Shanghai coven chemical co.,Ltd
17	Zomig	Zolmitriptan	Anti migrain	Headache	AstraZeneca
18	Salbutamol	Carmoisine	Antihhistaminic	COPD	Advacare

CONCLUSION:

Fast Dissolving Films have several advantages over the conventional dosage forms. They are considered as a most important drug delivery system today because of their rapid disintegration, improved dissolution. They combine the greater stability of a solid dosage form and good applicability of the liquid and thus bridge the gap between the two ideas, incorporating positive elements from both solid and liquid dosage forms into an elegant, stable and effective delivery vehicle. It is therefore of great importance in emergencies such as allergic reactions or asthma attacks, where immediate action is desired. As such, the technology is growing rapidly, challenging most pharmaceutical companies to develop oral films for a range of pharmaceuticals.

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