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Review Paper

FAST DISSOLVING FILMS (FDFs) AS A NEWER VENTURE IN FAST DISSOLVING DOSAGE FORMS

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ABSTRACT

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking water or chewing. More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patient's fear of chocking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot-melt extrusion. Thin film drug delivery, also referred to as orally dissolving thin film, and has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and OTC medications. Similar in size, shape and thickness to a postage stamp, thin film strips are typically designed for oral administration, with the person placing the strip on or under the tongue or along the inside of the cheek. Thin film enables the drug to be delivered to the blood stream either intragastrically, buccally or sublingually. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament. The 2-year-old, melt-in-your-mouth delivery system certainly has gained traction among consumers since the 2001 introduction of Pfizer's Listerine Pocket Packs. And now many OTC suppliers are banking on that consumer acceptance as they try to leverage the thin strip technology against a new generation of self-care remedies. There are currently several projects in development that will deliver prescription drugs utilizing the thin film dosage form.

Key words: *Fast dissolving films (FDFs), Oral strip, Disintegration, Dissolution.*

1. INTRODUCTION:

For the last two decades, there has been an enhanced demand for more patient-compliant dosage forms. As a result, there are now approximately 350 drug delivery corporations and 1000 medical device companies. The demand for their technologies was approximately $14–20 billion in 1995 and, according to industry reports; this is expected to grow to $60 billion [1, 2] annually.

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating [3], and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available[4].

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms.

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The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules [5]. An estimated 35% of the general population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy[6–9]. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in geriatric and paediatric patients, as well as travelling patients who may not have ready access to water [8].

1.1 Current Oral Fast-Dispersing Dosage Form Technologies:

Although several technologies are available, few have reached commercial marketed products. Table 1 shows the classification of these technologies according to core manufacturing processes. Several methods are employed in the preparation of oral fast-dispersing tablets, such as modified tableting systems, floss, or Shearform™ formation by application of centrifugal force and controlled temperature, and freeze drying.

Table 1: Current Oral fast-dispersing tablet technologies [10]:

Technology	Company
I. ***Conventional tablet processes with modifications***	
WOWTAB®	Yamanouchi Pharma Technologies, 1050 Arastradero Road, Palo Alto, CA, USA.
ORASOLV®	Cima Labs, Inc., 10000 Valley Hill Road, Eden Prairies, MN, USA
EFVDAS®	Elan Corp., Monksland Athlone, County Westmeath, Ireland.
FLASHTAB®	Prographarm, Chaueauneuf-En-Thymeraia, France
II. Freeze drying method	
ZYDIS®	R.P. Scherer, Frankland Road, Swindon, UK
LYOC®	Farmalyoc, 5AV Charles Marting, Maisons-Alfort,France
QUICKSOLV®	Janssen Pharmaceuticals, 1125 Trenton-Harbourton Road, Titusville, NJ, USA
III. Floss formation	
FLASHDOSE®	Fuisz Technologies, 14555 Avion At Lakeside, Chantilly, VA, USA

1.2 Classification Of Fast Dissolve Technology:

For ease of description, fast-dissolve technologies can be divided in to three broad groups:

1.2.1 Lyophilized systems,

1.2.2 Compressed tablet-based systems,

1.2.3 Thin film strips.

1.2.1 The lyophilized systems:

This system has been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural

excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration.

Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems.

1.2.2 Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard HDPE bottles or blisters through to more specialist pack designs for product protection – CIMA Labs', PackSolv, for example. The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail's Fuisz technology. It uses the proprietary Shearform system to produce drug-loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms. [11]

1.2.3 Oral Thin Films (OTF):

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery.

Dissolvable oral thin films (OTFs) or oral strip (OS) 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. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs [12].

This is largely as a result of the success of the consumer breath freshener products such as Listerine PocketPaks in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats [11].

1.2.3.1. Classification of Oral Film:

There are three different subtypes

(1) Flash release,

(2) Mucoadhesive melt-away wafer,

(3) Mucoadhesive sustained-release wafers.

These three types of oral films are differentiated from each other in following table 2.

Table 2: Types of wafers and their properties [13]

Property/Sub Type	Flash release water	Mucoadhesive melt-away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4
Thickness(µm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer system	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue(upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

1.2.3.2 Advantages of Oral Thin Film

This dosage form enjoys some distinct advantages over other oral formulations such as-

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.

2. The disadvantage of most ODT is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.

3. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.

4. Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids, tablets, and capsules. OTFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices [14].

5. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect [15].

6. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.

7 Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

8. OTFs are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs. The formulation of dissolvable films is customarily facilitated through aqueous polymer matrices that span a wide molecular weight (MW) range, thereby providing flexibility to achieve certain physical properties.

1.2.3.3 Disadvantage of Oral Strip

The disadvantage of OS is that high dose cannot be incorporated into the strip. However, research has proven that the concentration level of active can be

improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip [16].

There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly limits the range of compatible drug products.

The other technical challenge with these dosage forms is achieving Dose Uniformity [11].

1.7 Application of Oral Strip in Drug Delivery:

- Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs 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 oral thin films (OTFs) 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. application are shown in below figure.1

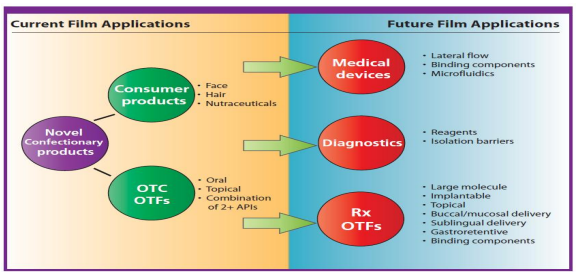

Fig.1. Evolution of dissolvable films. "OTC OTFs" are over-the-counter oral thin films. "APIs" are active pharmaceutical ingredients[12]

- **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 [17] 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 [18].

2. ORAL STRIP FORMULATION COMPONENTS

Formulation of OS involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc. The excipients used in formulation of OS are given below as per their categories. From the regulatory perspectives, all excipients used in the formulation of OS should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

2.1 Strip Forming Polymers

A variety of polymers are available for preparation of OS. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation [19]. On the other hand, fast dissolving strip dosage form should have the property to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously. Lists of polymers which are used in oral strip are given in Table 3.

Table -3 List of polymers used in oral strip formulation:

Pullulan	sodium carboxymethyl cellulose
gelatin	hydroxyl ethyl cellulose
Hydroxyl propyl methyl cellulose (hypromellose)	xanthan gum
Polyvinyl pyrrolidone(PVP)	locust bean gum
Modified starches	guar gum
Polyvinyl alcohol	carrageenan
Polyethylene oxide	Low viscocity grade HPC

As the strip forming polymer (which forms the platform for the OS) is the most essential and major component of the OS, at least 45%w/w of polymer should generally be present based on the total weight of dry OS [20]. Of the various polymers available, pullulan, gelatin and hypromellose are most commonly used for preparation of OS.

2.2. Plasticizers

Plasticizer is a vital ingredient of the OS formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer [21,22]. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. However inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip [23-25]. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug [26].The Plasticizer employed should impart the permanent flexibility to the strip and it depends on the volatile nature plasticizer and the type of interaction with the polymer. It should be noted that the properties of plasticizer are important to decrease the glass transition temperature of polymer in the range of 40–60 ºC for non aqueous solvent system and below 75 ºC for aqueous systems [25,27]. Plasticizer should be compatible with drug as well as other excipients used for preparation of strip [21]. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid [28]. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both Hypromellose as well as polyvinyl alcohol films [21].

2.3. Active pharmaceutical ingredient

In contrast the market for thin film strips is mainly in the consumer vitamins, minerals and supplements (VMS) and OTC areas. Active ingredients which appear to be suitable are vitamins, supplements such as melatonin and CoQ10, and some OTC ingredients. Examples of the type of developments in this area are the deals between Bioenvelop and NutriCorp, who have approval for a range of products in Canada including benzocaine, caffeine and menthol. To give another example, Leiner Health Products have an exclusive deal to sell MonoSol film strips for OTC products, the first of which is reported as a melatonin supplement.[11]

A number of molecules can be incorporated into this delivery system. They may include cough/cold remedies (antitussives, expectorants), sore throat,

erectile dysfunction drugs, antihistamines, antiasthmatics, gastrointestinal disorders, nausea, pain and CNS (e.g. anti-Parkinson's disease). Other applications comprise caffeine strips, snoring aid, multivitamins, sleeping aid etc.

The OS technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in OS. Generally 5%w/w to30%w/w of active pharmaceutical ingredients can be incorporated in the OS [29]. Multivitamins up to 10%w/w of dry film weight was incorporated in the OS with dissolution time of less than 60 s [30]. While water soluble APIs are present in the dissolved state in the OS or in the solid solution form, the water insoluble drugs are dispersed uniformly in the strip. The distribution of water insoluble molecules in water miscible polymer becomes important from the large scale manufacture point of view. Many APIs, which are potential candidates for OS technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the OS, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation [31]. The OS technology offers advantages in certain critical clinical situations. For drugs that are projected as local anesthetic or pain killer, the OS has demonstrated improved clinical benefits. Certain pathologies require instantaneous release of the medicament for prompt relief. For instance, in the case of migraine a rapid clinical effect is desired by the individual. Regiospecific delivery of the medicament would be required in the cases of sore throat, cough, allergy and other local oral manifestations. This dosage form can also be used for natural extracts and neutraceuticals including vitamin B12, chromium picolinate, melatonin and possibly CoQ10 [32]. Some of the examples of suitable drug molecule that can be incorporated in the OS are listed in following Table 4. [33]

Table 4. List of drug molecule that can be incorporated in the oral strip.

DRUG	Dose	Therapeutic class
Chlorpheniramine maleate	4 mg	Anti allergic
Triplolidine hydrochloride	2.5 mg	Anti histaminic
Loperamide	2 mg	Anti diarroheal
Famotidine	10 mg	Antacid
Azatidine maleate	1 mg	Anti histaminic
Sumatriptan succinate	35-70 mg	Anti migraine
Ketoprofen	12.5 mg	Analgesic
Nicotine	2 mg	Smoking cessation
Psuedoephedrine hydrochloride	30 mg	bronchodilator
Acrivastine	8 mg	Anti histaminic
Dextromethorphan Hydrochloride	10-20 mg	Cough supressant
loratadine	10 mg	Anti histaminic
Diphenhydramine hydrochloride	25 mg	Anti allergic

2.4. Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving

formulations. Suitable sweeteners include: (a) water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc (b) water soluble artificial sweetener: sodium or calcium saccharin salts, cyclamate salts,acesulfame-k etc (c) Dipeptide based sweetener: aspartame (d) protein based sweeteners:thaumatin I and II. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. [33, 34]

Aspartame was used for the preparation of oral strips of valdecoxib[35].For the oral strip of piroxicam, maltodextrin was employed as sweetening agent [36]. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination [33].

2.5. Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip. [34]

Other ingredients should be incorporated like sweetening agents, flavouring agents, coloring agents, stabilizing and thickening agents. Some time surfactant and emulsifying agents are also added in very minute quantity to manipulate film properties.

3. PHARMACOPOEIAL STATUS OF ORAL FILM

Monographs of common dosage forms are provided by the pharmacopoeias (e.g. Ph. Eur., USP). Even though dosage forms for application in the oral cavity such as Medicated chewing gums, Oromucosal preparations, Orodispersible tablets or oral Lyophilisates are included, monographs and specifications for oral films of diverse dissolution kinetics has not yet been established. There are inadequate pharmaceutical technical procedures for analysis in development and quality control of oral films as well. For instance, disintegration and dissolution testing procedures may be provided, but the recommended conditions such as volumes of media do not reflect the natural conditions in the oral cavity.

4. QUALITY CONTROL TESTS FOR FAST DISSOLVING FILM

Medicated strips are generally characterized by the quality control tests stated below.

4.1 Mechanical properties

All of the following mechanical properties like Thickness, Dryness test/tack tests, Tensile strength ,Percent elongation ,Tear resistance, Young's modulus , Folding endurance for prepared film should be evaluated as same as for plastic industry methodology. Further description for each parameter is briefly discussed elsewhere. [37]

4.2 **Disintegration time testing**

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips [38]. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s [39].Furthermore, a disintegration measurement setup for fast-dissolving oral dosage forms, in this

case ODTs, has been described but this setup cannot be transferred to oral wafers. For both methods only a small amount of medium is used, so natural conditions could be simulated. Due to the use of the Small amount of medium the dissolved drug substance could not be measured by spectral analysis.

(1) Slide frame method: one drop of distilled water was dropped by a Pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured.

(2) Petri dish methods: 2 mL of distilled water was placed in a Petri dish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely.[40]

4.3. 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 [41]. 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. R.C.Mashru et al used stainless steel wire mesh with sieve opening of approximately 700 µm used to dip salbutamol fast dissolving film inside the dissolution medium. [42]

4.4. Assay/drug content and 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%.

4.5. Organoleptic evaluation

Since the OS are intended to disintegrate rapidly or reside for more duration of time in the oral cavity, the product needs to have acceptable organoleptic palatable characteristics. For evaluation of psycho-physical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations [43]. Experiments using electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste-masking formulation [44].

4.6 Stability testing

For stability testing the oral wafers were stored under controlled conditions of 25 °C / 60 % RH as well as 40 °C / 75 % over a period of 12 months according to the ICH guideline [45].

During storage the oral wafers should be checked for their morphological properties, mass, thickness and reduction of film thickness, tensile properties, water content and dissolution behavior. Consecutively, pH and content during storage are displayed.

5. INFORMATION FOUND FOR FDFs FROM VARIOUS PATENTS STUDY

After reviewing various patents filled or issued for fast dissolving film we found that rapidly dissolving films are a novel dosage form hardly mentioned in the scientific world. The results from the patent search indicated that although a variety of excipients are used, some specific functional components for casting oral films are required. These main components include the film forming agents, the plasticizing agents, surfactants and solvents. Other excipients used are stabilizers, disintegrants, emulsifiers, bulk fillers, mouth feel improvers, cooling agents, flavors, fragrances, thickening

agents, preservatives and salivary stimulating agents as well as sweeteners. They are included in the formulation depending on the required properties. Furthermore, depending on the drug used, the excipients have to be adjusted to achieve desired properties such as a pleasant taste of the oral wafers.

6. MANUFACTURING METHODS FOR PRODUCING FDF

Various approaches to manufacturing of Rapid dissolving film are classified as follow:

6.1 Casting and Drying

(a) Solvent casting (b)Semi-Solid Casting

6.2 Extrusion

(a) Hot-Melt Extrusion (b)Solid Dispersion Extrusion

6.3 Freeze Dried Wafer

From above methods mainly solvent casting and hot-melt extrusion method is used for making fast dissolving film, so brief discussion of these two methods are given here.

6.1 Solvent-casting method

The RDF is preferably formulated using the solvent-casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution, and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size. Water-soluble hydrocolloids used to prepare RDFs include: hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), pullulan, sodium alginate, pectin, carboxy methyl cellulose (CMC) ,polyvinyl alcohol (PVA). Misao Nishimura et al used following procedure to produce the fast disintegrating film of prochlorperazine by solvent casting techniques. [41]

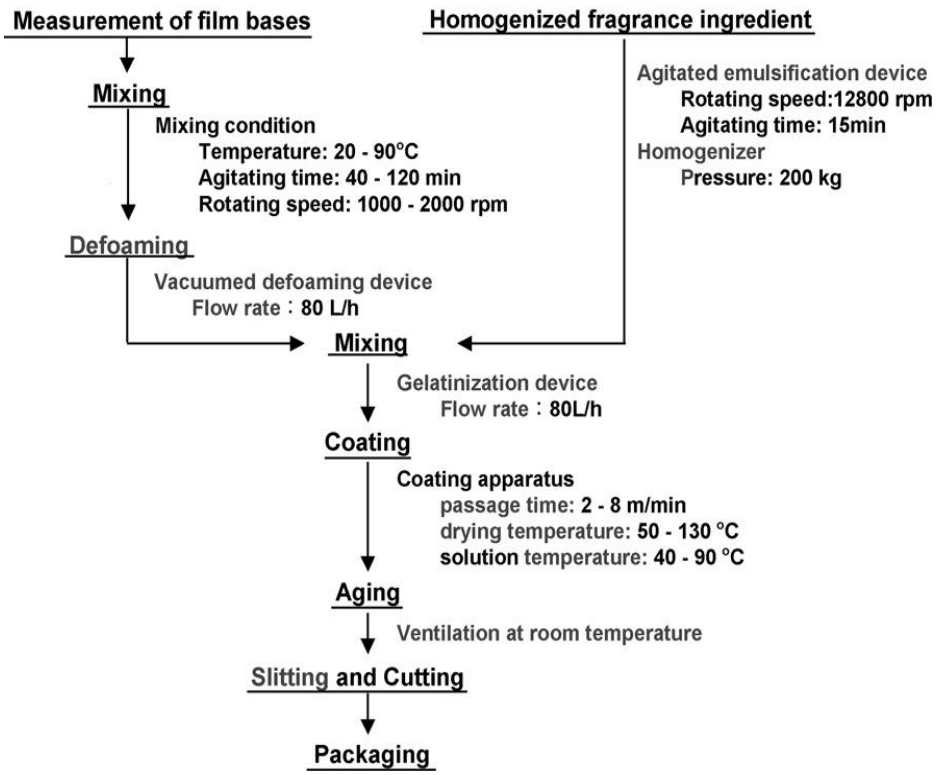

Fig.3 Flow chart of Procedures for the preparation of oral film (solution casting method)

Advantages:

Great uniformity of thickness and great clarity then extrusion A typical relative standard deviation (RSD) for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1–2% RSD.[39] Film have fine gloss and freedom from defects such as die lines. Film have more flexibility and better physical properties . The preferred finished film thickness is typically 12–100 μm, although various thicknesses are possible to meet API loading and dissolution needs.

Disadvantages:

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

Multiple casting techniques may be selected on the basis of the fluid rheology, desired applied mass, and required dosage uniformity.

6.2 Hot melt extrusion

Usually, when designing RDFs, polymers with low molecular weight or viscosity, such as HPMC E5 or pullulan PI–20, are preferred. A combination of various grades of polymers may also be used to achieve desired physical properties. Mixing polymers of high and low viscosity produces a film with good mechanical strength and high drug solubility in the film.

The manufacturing process for the wafers in the pharmaceutical industry is divided into different steps. Generally, the mass is prepared first under the control of temperature and steering speed. Afterwards, the wafers are coated and dried in a drying tunnel, once again the temperature, air circulation and line speed are controlled. Then follows a slitting and in the last step the wafers are punched, pouched and sealed. Other ways of manufacturing oral wafers are spraying process [46] or extrusion, in particular hot-melt extrusion [47, 48]

Advantages:

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.
- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages:

- Thermal process so drug/polymer stability problem
- Flow properties of the polymer are essential to processing
- Limited number of available polymers

7. STORAGE AND PACKAGING

The converting and packaging stage also provides product flexibility to drug manufacturers. The rolled film can be die-cut into any shape or size or slit into narrower rolls as required for the application. For branding purposes and to meet industry regulations, converters may choose to print information directly onto the film unit doses before packaging. Criteria that may be taken into consideration include the need for unit-dose packaging, barcode labeling, and the content in instructions for use, child-resistant seals, and senior-friendly packaging. [14]

8. MARKETING STATUS AND PRODUCTS AVAILABLE FOR ORAL THIN FILM DOSAGE FORM

The drug delivery sector of fast dissolve products has grown rapidly from sales in 2002 of about $850 million to 2005 were estimated sales were around $1.4 billion (IMS Data). [11] The lifestyle and

nutraceuticals market was the first to move into thin film format after breath fresheners with a range of fast dissolving strip products which incorporated actives such as vitamins, herbal extracts and non herbal extracts. The market for these types of product is in excess of $15bn worldwide. Currently, worldwide sales of drugs that incorporate a fast dissolve technology are more than $1 billion and have an annual growth rate of more than 40 per cent. This growth is fuelled by the patient demand, and industry estimates show that approximately 88 per cent of patients prefer taking medications that incorporate a fast dissolve any as 40 per cent of all people have difficulty swallowing traditional tablets.Nine launched OTF pharmaceutical products. In 2001 and 2002 it was reported that many significant therapeutic products would launch using this technology over the next two or three years. Whilst there has been a five-fold increase worldwide in the number of thin film strips since 2002, very few if any such products have entered the ethical prescription market. Forty-seven OTF products in the pipeline being developed by 12 companies Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion by 2010.TCI's report also details the technology programs of 25 companies active in the development of Orally-Disintegrating Tablet technologies and 17 active in the development of Oral Film technologies [48, 49].

8.1 List of Some Marketed Products available as FDF. [12,13,34]

Brand name	Manufacturer/distributor	API (strength)	Uses
Klonopin Wafers	Solvay Pharmaceuticals	Clonazepam (in five strengths: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg and 2 mg.)	Treatment of anxiety
Listerine Cool Mint Pocket Paks	Pfizer,Inc.	Cool mint	Mouth fresheners
Sudafed PE	Wolters Kluwer Health, Inc.	Phenylephrine	Relieving congestion
Suppress®	InnoZen®, Inc.	Menthol (2.5 mg)	cough suppressants
Triaminic	Novartis	Diphenhydramine HCL (12.5 mg)	Anti allergic
Theraflu	Novartis	Dextromethorphan HBR (15 mg)	Cough suppressant
Orajel	Del	Menthol/pectin (2 mg/30 mg)	Mouth ulcer
Gas-X	Novartis	Simethicone (62.5 mg)	Anti Flatuating
Chloraseptic	Prestige	Benzocaine/menthol (3 mg/3 mg)	Sore throat
Benadryl	Pfizer	Diphenyhdramine HCl (12.5 mg or 25 mg)	Anti allergic

9. CONCLUSION

Recently RDFs have gained popularity as dosage forms for the mouth freshners. Meanwhile pharmaceutical industries have recognized their potential for delivering medicinal products ad has launched several products for the OTC market using this technology. The fast dissolving thin film are hardly described and investigated in literature, but seem to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Due to lack of standard methodology for

preparation and analysis products existence in the market is limited.

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