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AN INNOVATIVE DOSAGE FORM FOR QUICK RELEASE "ORALLY DISINTEGRATING FILMS"

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Abstract:

Orally fast dissolving films have been introduced in the market recently as they provide convenience and ease of use over other dosage forms such as orally disintegrating tablets. Fast-dissolving oral delivery systems are solid dosage forms, which can disintegrate or dissolve within 1 min when placed on the tongue without drinking water or chewing. Oral route is the most preferred convenient route for drug administration due to the highest component of patient compliance mainly the pediatrics and geriatrics.

These are the formulation having thin film and larger surface area which is easily dissolves in the mouth saliva. Recently oral films containing breath freshener, vitamins supplement and API. These are formulated by incorporating the drug with selected oral cavity absorption enhancers in a specially designed oral dissolving film carriers. This facilitates the rapid absorption in the oral cavity for drugs with low GIT-bioavailability and intensive first-pass effects.

The unique property of orally disintegrating dosage form is that they are readily disintegrating and dissolves in saliva and mainly avoids the need of water which is the major benefit over conventional dosage form. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population.

This article discusses non-compliances issue in general, development of orally disintegrating films, their characteristics, advantages, formulation challenges, manufacturing methods, taste masking technologies, patients acceptance, evaluation and preference. Orally dissolving thin film has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and OTC medications.

Keywords: Orally disintegrating films, Pediartics, geriatrics, Solvent casting, Oral strips, Folding endurance, Water soluble polymers.

Introduction:

Oral route is most preferred route by medical practitioners and manufacturer due to its highest acceptability of patients. Oral administration is the most popular route due to its ability 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. A vast variety of pharmaceutical research is directed at developing new dosage form. Orally disintegrating dosage form is the widely preferred commercial product among the various dosage forms. The oral cavity is the most favorable site for administration of orally disintegrating dosage form due to the ease of ingestion. Conventationl tablet formulation are acquired 50 to 60 % market in medicine, according to this data the tablet formulation is most popular form but with this tablet having acceptance problem in the patients suffering from dysphagia, Parkinson's disease, mycosystis or vomiting, geriatric, bed ridden, psychotics and pediatric patient due to unwilling to take solid preparations due to fear of choking. Even with the fast dissolving tablet they having chocking problem due to the tablet appearance. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. So, mouth dissolving oral film drug delivery is a better alternative in such cases. Many drugs given orally have poor bioavailability conditions because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Traditionally, these drugs have been administered by parenteral route, which invariably lead to poor patient compliance. This made the pharmaceutical industries to look for alternative routes of drug delivery system. Intraoral fast-dissolving drug delivery system where in the dosage form (film) will be placed on the surface of the tongue or in the oral/buccal cavity, then drug release rapidly for local and systemic absorption. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating. However, the function and concept of all these dosage forms are similar. Over the last few decades, pharmaceutical industries put a lot of effort to innovate on drug delivery systems. A patient friendly, economical and yet effective drug delivery system, is needed to provide a solution to the non-compliance issue. One of the novel inventions is oral disintegrating dosage form, namely orally

disintegrating film (ODF). The demand for orally disintegrating dosage form has increased in market, so it has significant impact on the patient compliance.

Orally Disintegrating Films:

Oral films, are also called as oral wafers in the related literature, are a group of flat films which can be administered into the oral cavity [1,12]. Although oral film systems have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. They are thin elegant films of edible water-soluble polymers of various shape and sizes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. Fast disintegrating films (FDFs) have a large specific surface area for disintegration [6,20]. The films alleviate the danger/ fear of chocking, easy to handle and administer, maintain a simple and conventional packaging that is easy to manufacture thus overcoming the short falls of oral fast disintegrating tablets. It is intended to be placed on patient's tongue. When film is moistened with saliva, it rapidly moistened and disintegrates to release the active ingredient for mucosal absorption or gastrointestinal absorption after swallowing. ODF starts to gain recognition as a consumer friendly dosage form since the early 21st century, with the introduction and widespread use of Listerine pocket strips, a new launch in the mouthwash range [12,34].

Concept of Orally Disintegrating Film [7,22,59]:

1. It consists of a thin film.
2. When film is put on the top of the tongue, it dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and thus increases the bioavailability of drug.
3. It dissolves in the oral cavity like a cotton candy.

Special Features of Mouth Dissolving Films [49,54]:

1. Good mucoadhesion
2. Post stamp size
3. Flexible and infragile
4. Taste masked
5. Available in various size and shapes
6. Unobstructive

7. Fast disintegration and dissolving time.
8. Ultra thin

Rationale in the Selection of the Dosage Form:

Orally disintegrating films are the novel approach to attain fast onset of action and immediate relief from the symptoms [48,53]. Moreover in geriatric patients have difficulty of swallowing. Hence, fast dissolving films are the best formulations as these are soluble in simulated salivary fluid with in 1 minute releasing the drug and inactive ingredients. Most of the drug is swallowed with saliva where rapid absorption takes place in gastrointestinal tract [1,5].

Classification of Oral Films [39]:

There are three different subtypes

1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained-release wafers

Table-1: Types of Wafers and their Properties [17,33,60]

Sub type	Flash Release Wafer	Mucoadhesive Melt-away	Mucoadhesive Sustained release
Area $(cm)^2$	2-8	2-7	2-4
Thickness	20-7	50-500	50-250
Structure	Film: single layer	Single or multilayer	Multi layer system
Excipients	Soluble	Soluble	Non-soluble Polymers
Drug phase	Solid solution	Solid solution	Suspension
Application	Tongue	Gingival/ buccal Region	Gingival
Dissolution	Max 60 seconds	few minutes	Maximum 8-10 Hrs

The ideal Characteristics of a Drug to be selected [16,31,47]:

1. It should have pleasant taste.
2. Drug to be incorporated should have low dose up to 40 mg.
3. Drugs with moderate molecular weight are preferable.
4. It should have good stability and solubility in water as well as in saliva.
5. Drug should be partially unionized at the pH of oral cavity.
6. Drug should have the ability to permeate oral mucosal tissue.

Advantage of Orally Fast Dissolving Films [27,46,57]:

1. Orally disintegrating films can be taken without usage of water at any time and at any place.
2. It leads to rapid disintegrating and dissolution in the oral cavity due to its availability to larger surface area.
3. Avoidance of first pass effect due to which drug should be improves potency by the sublingual route with low dose high efficacy and less side effect.
4. It should be beneficial in cases such as motion sickness, acute pain, coughing where an ultra fast onset of action required.
5. It will help to solve the non-compliance issue from the health care provider's point of view. Hence, the health care cost should be reduced.
6. As compared to liquid formulations, precision and accuracy in the administered dose is ensured from each strip of the film.
7. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to avoidance side effects.
8. As compared to drops or syrup formulations, precisionand accuracy in the administered dose is ensured from each of the strips.
9. It provides new business opportunity like product differentiation, product promotion, patent extension etc.
10. From the marketing point of view, a patented ODF technology is beneficial and helpful to the company to obtain more benefit.

Disadvantages of Orally Disintegrating Films [43,51]:

Films cannot be formulated into high dosage form.

1. Expensive packaging of oral films because these are temperature and moisture sensitive.
2. Dose uniformity in the formulation of film is a challenging problem.

Application of Oral strip in Drug delivery:

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of orally disintegrating films could become a primary delivery method for therapies where fast onset of action is required, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders [14,19].

Dissolvable oral thin films became a novel and widely accepted form by consumers for delivering vitamins and personal care products [30,56].

Common Examples of Patented ODF Product [2,9,11]:

There are various ODF products that have been patented.

Table-2: Examples of ODF Products in the Market

Product	Drugs	Manufacture
Theraflu Thin Strips Long Acting Cough	Dextromethorphan	Novartis
Theraflu Thin Strips Multi-Symptom	Diphenhydramine	Novartis
ThaminicThin Strips Long Acting Cough	Dextromethorphan	Novartis
Triaminic Thin Strips Cough & Runny Nose	Diphenhydramine	Novartis
Gas-X Thin Strip Anti Gas	Simethicone	Novartis
Little Colds Sore Throat Strips	Pectin	Prestige Brands
Suppress Cough Strips	Dextromethorphan	InnoZen
Suppress Herbal Cough Relief Strips	Menthol	InnoZen

Formulation Considerations:

Orally films formulation consist the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc [21,34,35]. From the regulatory perspectives, the excipients commonly used in the formulation of orally disintegrating films should be generally safe and should be approved for use in oral pharmaceutical dosage forms [28,32].

A typical composition contains the following:

Following general composition of drug & excipients in percentage [44,56]:

1. Drug ----- 05% to30%w/w
2. Water soluble polymer ----- 45%w/w
3. Plasticizers ----- 0-20%w/w

4. Surfactants ----- q.s.
5. Sweetening agent ----- 3 to 6 %w/w
6. Saliva stimulating agent ----- 2 to 6%w/w
7. Fillers, colors, flavors etc. ----- q.s.

Table-3: Excipients generally used in Preparation of Orally Disintegrating Films [3,10,43]

Ingredient/ Purpose	Examples	%(w/w)
Water soluble polymers	Cellulose ethers (HPMC, HEC, HPC, and MC), PVC, PVA, gelatin, Pullulan, kollicoat IR, PEG, tragacanth gum etc.	40-50
Plasticizers	Glycerol, PG, PEG	0-20
Disintegrants	Pregelatinised starch, MCC etc.	0-40
Preservatives	Salts of edetate (disodium EDTA)	.01-1
Saliva stimulating agents	Citric Acid, lactic, malic acid , succinic, ascorbic, adipic, fumaric and tartaric acid	2.5-6
Cooling agents	Monomethyl succinate	.2-.4
Surfactants	Mono & diglycerides of FA, polyoxy ethylene sorbitol esters	.5-15
Stabilizing agents	Xanthan gum, locust Bean gum and carrageenan	.1-2
Emulsifying agents	Triethanolamine Stearate, Qt.Ammonium Compounds, Acacia, gelatin	.1-0.7
Thickening agents	MC, carboxy methyl cellulose	.01-5
Sweetening agents	Sucralose, aspartame, Acesulfame K, Neotame	0-2

1. Active Pharmaceutical Ingredient:

A typical film composition contains 1-25% of the drug [4,7]. Wide varieties of APIs can be delivered through fast dissolving films. API generally 5mg to 30mg can be incorporated into the film. Insoluble API is dispersed uniformly in the film. APIs can also be added as milled, micronized and also in the form of nanocrystals or particles depending upon the ultimate release profile [22,27]. APIs mainly used for oral film technology are with bitter taste which makes the formulation unpleasant, especially for pediatric formulations [20].

Various methods can be used to improve palatability of the formulation:

1. **Simplest method:**

It involves the mixing and blending of bitter tasting API with pleasurable taste which is known as obscuration technique.

2. **Barrier method**

It can be used to mask the bitter taste which includes complexation, polymeric coating and micro particle and coated particle.

2. Film Forming Polymer:

Formation of film required film forming polymer which is having low molecular weight, if not it will affect on the disintegration time of the film. Generally natural gums are used as water soluble polymer derived from acacia, Arabic or tragacanth, guar, xanthun other available polymers are, acrylic based polymer polyethylene oxide, and several types of sodium carboxymethyl cellulose (CMC), several types of hydroxypropyl methyl cellulose (HPMC) [10,17,41]. The polymer used should be non-toxic, non-irritant and devoid of leachable impurities. It attains good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be easily available and should not be very expensive. Pullulan is a naturally occurring polymer obtained from non-animal region and does not require chemical modification. Modified starches are also used for preparation of orally disintegrating films [38,42]. It is used in the combination of pullulans due to the low cost of these excipients to decrease the overall cost of the product [21,23]. Combination of microcrystalline cellulose and maltodextrin has been used to formulate orally disintegrating films. As the most essential and major component of the Oral Film, film forming polymer (which forms the platform for the Oral Film) is used ,at least 45%w/w of polymer should generally be present based on the total weight of dry Oral Film [5].

Table 4: List of Polymers used in Formulation [37,44,46]

Polymers	Use
Pullulan	Modified starches
Gelatin	hydroxyl ethyl cellulose
Hydroxyl propyl methyl cellulose	Xanthan gum
Polyvinyl pyrrolidone	locust bean gum
Sodium Carboxymethyl cellulose	Guar gum
Polyvinyl alcohol	Carrageenan
Polyethylene oxide	Low viscosity grade HPC

3. Plasticizers:

It improves the flexibility of the strip and reduces the brittleness of the strip. It improves the properties of strip by reducing the glass transition temperature of the polymer [52]. The plasticizer selection will depend upon its compatibility with the polymer and also the type of the solvent used in the casting of the strip. Plasticizer should be compatible with drug as well as other excipients used for preparation of strip. 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 [49,56]. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both Hypromellose as well as polyvinyl alcohol films. It is also seen that the use of certain plasticizer may also affect the absorption rate of the drug. Typically, plasticizers are used in the concentration of 0–20 percent w/w of dry polymer weight. However, inadequate use of plasticizer may lead to film peeling, cracking and splitting of the strip [7,9].

4. Sweetening Agents:

Sweeteners have become the important part of the food products as well as pharmaceutical products required to be disintegrated in the oral cavity [15,33]. The sweet taste in formulation is more essential in case of pediatric population. The main sources of sweetener are sucrose, dextrose, fructose, liquid glucose, glucose and isomaltose. The sweetener of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and isomalt can be used in combination as they additionally provide good mouth-feel and cooling

sensation [35,60]. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose [16,23]. For suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron sucralose and neotame were generally used [26]. Generally sweeteners are used in the concentration of 3 to 6 %w/w. Rebiana which is a herbal sweetener, derived from plant known as Stevia rebaudiana has more than 200-300 time sweeteners.

5. Saliva Stimulating agent:

Saliva stimulating agents is used to increase the rate of production of saliva results in faster disintegration of the quick dissolving strip formulations. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants [59].Citric acid being the mostly used amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip. Generally acids commonly used in the preparation of food can be used as salivary stimulants [29,45].

6. Flavoring agents:

Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. These can be used alone or in the combination. Peppermint oil, cinnamon oil, oil of nutmeg are examples of flavoring agents [29,44]. The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and after taste of the formulation which lasts for at least about 10 min. The selection of flavor is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness [51,54]. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc.The amount of flavor needed to mask the taste depends on the flavor type and its strength. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.

Table-5: Flavoring agents for Taste masking [4,18,32]

Basic Taste	Recommended Flavors

Salt	Butterscotch, apricot, peach, wintergreen mint.
Butter	Wild cherry, walnut, chocolate, mint, anise.
Sweet	Vanilla, fruit and berry.
Sour	Citrus flavor, licorice, root beer, raspberry.

7. Surfactants:

It can be used as solubilizing/wetting/ dispersing agent in film formation so that the film is getting dissolved within seconds and release active agent quickly [19,41]. Most of the commonly used agents are sodium lauryl sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

8. Colouring Agents:

Colouring agents approved by F D & C are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. Eg. Titanium dioxide [30].

Method of Preparation:

Orally disintegrating films are formulated by following methods:

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

1. Solvent casting Method:

In this method, to form clear viscous solution water soluble polymer are dissolved in water [18,40]. 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. Finally solution is casted in to the Petri plate and dried [39]. Then degassed the viscous material by sonicator coated on film base. The coated air is to send oven for drying the film. Then the film is cut into different shape. Film thickness is measured by screw gauze. In these method material is make viscous then mix homogeneously and evaporates solvent at high temperature [8,11].

Advantages [8,42]:

1. Film has fine gloss and free from defects such as die lines.
2. Better uniformity of thickness and bitter clarity is achieved.
3. Film has more flexibility and good physical properties.

Disadvantages [30.41]:

1. The polymer must be soluble in a volatile solvent or water.
2. A stable solution is formed, with a reasonable minimum solid content and viscosity.
3. Formation of a homogeneous film.

2. Semisolid casting Method:

In this method, first of all solution of water soluble film forming polymer is prepared [13,25]. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then adequate amount of plasticizer is added into it. The gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide [53,55]. Acid-insoluble polymers are used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer with film forming polymer ratio is 1:4 and film thickness is 0.015 to 0.05 inches.

3. Solid dispersion Extrusion:

In solid dispersion extrusion method immiscible components is extrude with drugs and then solid dispersions are prepared [3,40]. Finally the solid dispersions are shaped into various size of films by means of dies.

4. Hot melt Extrusion:

In Hot melt extrusion method, drug is mixed with carrier in the solid form. Then the dried granular material is introduced into the extruder [15].The screw speed should be set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3–4 min. The processing temperatures should be 80ºC (zone 1), 115ºC (zone 2), 100ºC (zone 3) and 65ºC (zone 4). The extrudate (T = 65ºC) then pressed into a cylindrical calendar to obtained a good film. Then follows a slitting and in the last step the films are punched, pouched and sealed. Formulated Piroxicam film with Maltodextrin plasticized by glycerin by using Hot melt extrusion method [31].

Advantages [24,26]:

1. In this method, homogeneous distribution of fine particle occurs.

2. Compressibility properties of the API are not important.
3. Content uniformity was better.
4. During processing, solvents and water are not required.
5. Less processing steps.
6. Less energy required.
7. Cost-effective process with reduced production time and number of unit operations.
8. It is an anhydrous process.

Disadvantages [14,28]:

1. Few numbers of polymers are available.
2. Thermal degradation occurs due to use of high temperature
3. Lower-melting-point binder risks situations in which melting or softening of the binder occurs during handling and storage of the agglomerates.

5. Rolling Method: In this method, suspension or solution containing drug is rolled on a carrier [36,50]. The solution or suspension should have a specific rheological consideration .The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes [58].

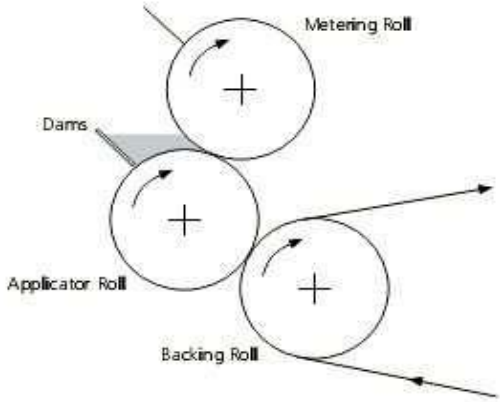

Fig-1: Three roll coating unit.

Evaluation of the Film:

1. Morphology study:

To study the morphology of films, electron microscopic (SEM) at definite magnification is used. [52,57]

2. Weight Variations:

It is studied by individually weighing 10 randomly selected films and calculated the average weight. It should not deviate from the average weight.

3. Film thickness:

Film thickness can be calculated by using micrometer screw gauge. It is very essential to determine the uniformity of film thickness [2,37]. It is directly related to the accuracy of dose in the film. It can be measured by micrometer screw gauge or calibrated digital Vernier Calipers**.** Three readings from all the batches were measured and mean thickness was calculated.

4. Drug content:

A film of size 2 × 2 cm was cut and put 10 ml of volumetric flask which containing solvent. It is then shaken in a mechanical shaker for 2 hrs to get a homogeneous solution and then filtered. Then the drug was determined spectroscopically [6,38].

5. Tensile strength:

It is the maximum stress which can be applied to a point at which the strip specimen breaks [13,25]. It is calculated by the applied load at rupture divided by the cross-sectional area of the strips.

Tensile strength = Load at breakage/ Strip thickness × Strip Width

6. Percent elongation: Strain is basically the deformation of strip divided by original dimension of the sample. Normally, elongation of strip increases with the increase in plasticizer content [24,36]. When stress is applied, a strip sample stretches and this is referred to as strain.

% Elongation = Increase in length/original length×100

7. Folding endurance: It is the number of times the film is folded without breaking. The evaluation of films involves determining the folding capacity of the films when subjected to continue extreme condition of folding [47,59].It is determined by repeated folding of the film at the same place till it breaks.

8. Swelling property:

For checking the swelling properties of the oral film, saliva solution is used [1]. Each film sample is weighed and it is placed in a preweighed stainless steel wire mesh. The mesh containing film sample is then submerged into 15ml medium in a plastic container. Weigh the film after specific time up to constant weight of film is come.

Degree swelling property is calculated by following formula:

SI = wt – wo / wo

wt is weight of film at time

t, and wo is weight of film at time zero.

9. Transparency:

It can be determined using a simple UV spectrophotometer. For this, cut the film samples into rectangles and placed it on the internal side of the spectrophotometer cell [48,53]. The transparency of the films was calculated by following formulae:

Transparency = (logT600)/b = - €c

Where T600 is the transmittance at 600 nm

b= film thickness (mm)

c =concentration

10. Dryness test/tack tests:

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-to touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films. Various instruments are also available for this study [50,58].

11. Tear resistance:

Tear resistance of plastic film is defined as a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm is employed and is designed to measure the force to initiate tearing [6,19]. The maximum force required to tear the specimen is termed as the tear resistance value. It is expressed in Newtons.

12. Young's modulus:

It 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 [34,55]:

Young's modulus = Slope × 100/Strip thickness × Cross-head speed

13. Surface pH:

To check the risk of any side effects in vivo, the surface pH of the oral dissolving film is calculated. Since acidic or alkaline pH may cause irritation to the oral mucosa, so it is determined to maintain the surface pH as close to neutral as possible [12,37]. A combined pH electrode is used for this purpose. The surface pH of the films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. Change in the colour of pH paper was observed and reported [9].

14. Contact angle: It can be measured by goniometer (AB Lorentzen and Wettre, Germany) .In this method, double distilled water drop is place on dry film [45,51].Then digital picture is take within 10 second of drop add on film

analyzed by image for angle determination. Minimum five times at different position is used to check the contact angle film.

15. Organoleptic evaluation:

For psychophysical evaluation of the product, special controlled human taste panels are used. Specially designed apparatus are used to check the in-vitro methods of utilizing taste sensors. Modified pharmacopoeial methods are being used for this purpose [10,34].

16. Assay/ Content uniformity:

Content uniformity is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia [18,35]. It is determined by calculating the API content in individual strip. Limit of content uniformity is 85–115 percent.

17. In vitro disintegration time:

In vitro disintegrating test is done to find out the actual time required for disintegration of the film. It needs USP disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips [27,39]. Disintegration time can be vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. In vivo disintegration test take the volunteer (n =6) and then place the film in the mouth of volunteer and check the time required for its disintegration [5].

18. In vitro Dissolution test:

Dissolution studies of films were performed by USP XXIII type II apparatus [59].These requires distilled water, 6.8 phosphate buffer (300ml) and 0.1N HCl (900ml). The temperature (37±0.5°C) and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analyzed spectrophotometrically. The dissolution test can be difficult many times while operating with paddle apparatus due to tendency of the strip to float onto the dissolution medium [46].

19. Permeation studies:

Permeation studies are done using modified Franz diffusion cell by using porcine buccal mucosa. Buccal mucosa is kept in between the donor and receptor compartment of Franz diffusion cell [29]. In receptor compartment, Fill buffer kept at 37 °C ± 0.2 °C and maintain the hydrodynamics by using magnetic stirring at 50 rpm. On buccal mucosa the oral disintegrating film is placed before placing mucosa will be moisten by few drop of simulated saliva, in the donor

compartment and then added 1ml of simulated saliva of pH 6.8 [11]. Samples withdraw at specific time interval fill with same amount of fluid to maintain the sink condition. Then percentage of drug permitted is calculated by taking absorbance by U.V method [18,35].

20. Stability studies:

Stability studies are conducted at accelerated condition of 65% relative humidity and 35 ºC temperature in the humidity chamber for the three months [18,45]. Films are evaluated for the drug content, disintegration time and physical appearance after 3 months.

21. Taste evaluation:

In-vivo test evaluation studies going with panel of volunteers and In -vitro studies by using the test sensor analyze the sweetness level of taste masking agent [46,53].

Different Technology used in Orally Disintegrating Films formulation:

1. XGel: It is developed by Bio-progress. These technologies cause a revolution in the product offerings and manufacturing methods are available to the pharmaceutical industry [17,38].

2. Foam burst: It is a new patent granted in September 2004 .It is used for capsule made of foamed film. Gas is blown into the film during production, resulting in a film with a honey combed structure [43,52]. The Light honey combed structure results in capsule that dissolve rapidly, causing a melt-in-the mouth sensation. Voids are empty or filled with other material to acquire the specific taste or odour.

3. Micap: Micap is used in micro encapsulation technology with the Bio progress water-soluble films [12,30]. Micap plc signed an option agreement in 2004 to combine its experts. Formation of smoke sensation product is the main aim of this company.

4. Soluleaves:

SOLULEAVES technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form [44,58]. It is used to formulate the quick dissolving films by adding with active ingredient, flavor and colours. This is applied to flavour-release products such as mouth fresheners, confectionery and vitamin products.

5. Wafertab:

It is a patented delivery system which requires a unique process to prepare drug loaded thin film and it is used for topical or oral application [6,27]. Active ingredients are incorporated into the film after casting.

Table-6: Examples of Marketed Oral Thin Films [41,52,58]

Brand name	Manufacturer	API (strength)	Uses
Klonopin Wafers	Solvay Pharmaceuticals	Clonazepam(.125, 0.25, 0.5, and 2 mg.)	Treatment of anxiety
Suppress®	InnoZen®, Inc	Menthol (2.5 mg)	Cough suppressants
Triaminic	Novartis	Diphenhydramine HCL	Anti allergic
Theraflu	Novartis	Dextromethorphan HBR (15 mg)	Cough suppressants
Orajel	Del	Menthol/pectin	Mouth ulcer
Gas-X	Novartis	Simethicone	AntiFlatuating
Chloraseptic	Prestige	Benzocain	Sore throat

Packaging Technique:

SoluStrip™ with its soluble film strip in a pouch is an ideal delivery format for OTC and Rx drugs whether oral, mucosal, or topical, and may even offer extended patent protection for brand [22,49]. Soluble films strip can also deliver vitamins and nutraceuticals, flavors or fragrances and these are also well known for their oral care applications such as tooth whiteners [7,50]. These are not only limited to edible and oral applications. Soluble film is also applicable for topical skin care treatments, cosmetics, and numerous general household applications [8,36]. It may be a unique product or as an adjuvant to other products to deliver visible value. Film having unique ingredients including vitamins, minerals, special flavoring and colouring agents [39]. These films can be cut into various shapes or sizes and then they are added to gels, lotions, creams or other products to supply ingredients that can be easily used by customers [28].

Conclusion:

Orally disintegrating films are revolutionary and innovative drug delivery systems for all the population specifically geriatric, pediatric and patients with swallowing difficulties although these are not well defined in the literature. Recently ODFs have gained popularity worldwide as a dosage forms used for mouth freshener. By using this

technology, pharmaceutical industries have recognized their benefits for delivering medicinal products and launched several products for the OTC market [44,58]. Orally disintegrating films are also having great potential of delivering the medicinal agent systemically as well locally. Orally disintegrating film has several advantages over many dosage forms such as fast disintegrating tablets. Due to low cost, patient compliance is more. Better mouths feel than other formulation. It avoids first pass metabolism and degradation occurs into the gastro intestinal tract. Therefore orally disintegrating films are an accepted technology for systemic delivery of API's. Orally disintegrating films have several advantages over the conventional dosage forms. So, they are of great importance during the emergency condition like allergy. So, orally disintegrating films have evolved as consumer friendly dosage forms. So many of the pharmaceutical companies are launching this technology as formulation of these films occurs through non-sophisticated, uncomplicated equipment and procedures [46]. Due to these, orally disintegrating films have economically feasible developmental futuristic opportunities.

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