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Overview of Orally Disintegrating Film.

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ABSTRACT

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for the patients of pediatric and geriatric who faces difficulties in swallowing conventional oral solid dosage forms. On the basis of this need, a variety of orally disintegrating tablet (ODT) formats were commercialized. Most ODT products were formulated to disintegrate in less than one minute when placed in mouth (saliva) to form a solution that could then be more easily swallowed. 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 personal care products and vitamins. Companies having 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 accepted proven 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. This review article provides the basic overview regarding to the importance, advantages, disadvantages, formulation, preparation, evaluation and patents related to the orally disintegrating film (ODFs).

Keywords: Active pharmaceutical Ingredients, Fast dissolving films, Oral Thin Film, Orally disintegrating films, Over the Counter medications

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INTRODUCTION

Fast dissolving drug delivery system (FDDS) was introduced in late 1970 as the alternative to conventional tablet, capsule and syrups especially for the geriatric and pediatric patients who generally suffer from the dysphasia problem [1]. Fast dissolving tablets are the solid dosage form which disintegrates rapidly in the oral cavity without the need of water [2-3].Recent developments in the technology produces viable dosage forms, alternative to oral route for the pediatric, geriatric, bedridden, nauseous or noncompliant patients. Buccal delivery is modern technology in that bioadesive dosage form have been produced as an adhesive tablet, gel, patches, ointment, more recently, using polymeric film – called as mouth dissolving films[4]. Conventional tablet formulations have acquired the 50 to 60 % market[5] in medicine, according to this data the tablet formulation is the most popular form but faces acceptance problem in the patients suffering from Parkinson's disease, dysphagia, mycosystis or vomiting, geriatric, bed ridden, psychotics and pediatric patient due to unwillingness to consume solid preparations due to fear of choking. Even with the fast dissolving tablet they are having chocking problem (psychological) due to their tablet appearance. According to survey out of 100 patients 26 patients shows non acceptance to tablet due to their swallowing disability, tablet size, surface form and taste. The problem of swallowing tablets is more profound in pediatrician geriatric patients, as well as travelling patients who may not have immediate access to water [6-7].Due to this problem; new development in conventional tablets by using super disintegrants was put forth. Researchers produced wafer is the recent development of oral fast dissolving films (OFDF) [8]. This newly developed drug delivery system can also be beneficial for meeting the current needs of the industry& also beneficial to improve solubility/stability, bioavailability enhancement &biological half life of drugs. New additions in the Oro dispersible film preparations are Metoclopramide (5mg), Dextromethorphan HBr, Nicotine (Nicabate film),Diphenhydramine HCl, Simethicone, Phenylephrine HCl, and Benzocaine Menthol [9].

Saliva is a secretion of three salivary glands (parotid, submandibular and sublingual) present in the oral cavity [10]. Saliva is relatively less viscous compared to GI fluids [10-11]. It mainly contains water and 1% organic and inorganic material and is a weak buffer having pH ranges from 5.5-7.The total volume of saliva secreted from the salivary gland is 0.5-2 liters and it is enough to hydrate oral mucosal dosage form [12-13]. Oral films rapidly disintegrate within seconds when it comes in contact with saliva without the need of water.

Types of Mouth dissolving Film

- Flash release film
- Flash dispersible film
- Non disintegrating mucoadhesive film
- Medium disintegrating mucoadhesive film

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Advantages of oral disintegrating films [14-16]

- Rapid disintegration than orally disintegrating tablet due to larger surface area of the film.
- Orally disintegrating tablets are having fragile and brittle nature due to which they require special packing against the transport, but ODFare flexible films and non-fragile in nature.
- ODFs are recently formed materials and are mostly accepted for the OTC (over the counter) products over conventional products having accurate dose in the safe and effective format and no need of water while consuming.
- Patients of dysphasia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.
- For drug showing first pass metabolism , ODF have advantage because oral or buccalmucosa is highly vascularised, that's why drug get absorbed directly in to the systemic circulation improving efficacy with low dose and less side effect.
- No special training is required for the administration of the dosage form.
- Site specific and rapid onset of action.

Disadvantage of Oral disintegrating films [17-19]

- Drugs with high dose cannot been incorporated.
- Special type of packing is required due to its moisture and temperature sensitivity.
- Dose may vary throughout the film.

Special features of oral films [17-20]

- Ultra-thin films
- Available in various size and shape
- Unobstructive
- Rapid release and fast disintegration
- Excellent mucoadhesion

Table 1: Patents related to Orodispersible films[23-29]

Country	Patent No.	Title	Inventor
US	0216594 A1	Preparation of Orodispersible films	Andreas Krekeler
US	7560429 B2	Orodispersible dosage forms of Desmopressin acetate	Anders Nilsson, Lund (SE); Hans Lindner,
US	7201922 B2	Orodispersible solid pharmaceutical form	Michel serpellonis BeuVI-y_1eS_Bethune[FR]
US	6596298 B2	Fast dissolving orally consumable Films	Sau-Hung Spence Leung, Parsippany, NJ (US); Robert S. Leone,
US	7132113B2	Flavoured film	Zerbe et.sl
US	7241411B2	Thin film strip	Berry et.al
US	6824829B2	Process for manufacturing thin film strip	Berry et.al

Formulation consideration [30-31]:

From the regulatory prospective all the excipients used in the formulation and development of oral films and they are regarded as safe (GRAS listed) and should be approved for use in oral pharmaceutical dosage forms. The area of oral thin films is 1-20cm^2(depend on dose and drug loading containing drug).

Drug (Active pharmaceutical ingredient) [32]:

Different type of API can be successfully incorporated in the oral strip technology. Micronized API can improve the texture of the film and also dissolution and uniformity of the oral fast dissolving film. Taste of bitter drug need to be masked for that Cyclodextrins or resins can be used [33-37]. It include cough/cold remedies(antitussive, expectorants), anxiety drugs, CVS agent, sore throat, erective dysfunction drugs, antihistamines, antiasthamatics, GI disorders, nausea, pain and CNS (antiparkinson's) disease.

The unique properties of drug for the development of oral strips formulation:

- The drug should have low dose.
- The dug have extensive high first pass metabolism.
- It should not be bitter.
- It should have quick onset of action.
- The dug should have high solubility and high permeability (BCS class I).

Polymers [38-41]:

Polymers play an important role in the film formation. Hydrophilic polymers are used in the preparation so that film can dissolve rapidly in the oral cavity and drug is delivered to the systemic circulation via dissolution when it comes in contact with the saliva in the buccal cavity [42]. The polymers can be used alone or in combination in a film to get the desired film properties. Robustness of film depends on the type and amount of polymer in the formulation. These days both natural and synthetic polymers are used in the delivery system meant for oral cavity. Natural polymers are safe, effective and devoid of side effects& more preferred than synthetic polymers.

Ideal properties of the polymers used in the oral film [43]:

- Polymers should be non toxic and non- irritant
- It should be non- bitter
- Polymers should be tasteless
- It should be devoid of leachable impurities
- It should be inexpensive and readily available
- It should not be an obstacle in the disintegration time

- It should have good wetting and spreadibility property
- It should exhibit sufficient peel, tensile strength and shear
- It should have sufficient shelf life
- It should not cause secondary infection in the oral cavity.

Plasticizer [44-55]:

Plasticizers are the important excipient of the oral film. It improves the flexibility and a mechanical property of the film like tensile strength and elongation and reduces the brittleness of the strip. Plasticizer significantly improves the properties of strip by reducing the glass transition temperature of the polymer. A plasticizer selected, must be compatible with the drug, polymers as well as with the other excipients used in the oral film. Plasticizer can improve the flow and enhances the strength of polymer. Film cracking, splitting and peeling take place by the use of inappropriate plasticizer. Plasticizers are used in the concentration of 0–20%w/w of dry polymer weight. Common plasticizers used in the preparation of the oral films are Glycerol, propylene glycol, polyethylene glycol, dimethyl, dibutyl, diethyl phthalate, tributyl, triethyl, actyl citrate, triacetin and castor oil.

Sweetening Agents [56-64]:

Sweeteners are the important component used in the oral films. Mostly sweeteners are used for the taste masking of bitter drugs so that drugs are palatable. Sweeteners are used alone or in combination between the concentrations of 3-6%w/w. Natural as well as artificial sweeteners are used in the preparation of oral film. Natural sweeteners used are xylose, ribose, glucose, sucrose, maltose, steviosides, dextrose, fructose, liq. Glucose and isomaltose.Fructose is sweeter than sorbitol and mannitol and thus widely used as a sweetener. Artificial sweeteners used in oral films are sodium or calcium saccharine salts, cyclamates salts, Acesulfame k etc. Acesulfamek and sucralose are more than 200 & 600 times sweet. Neotame & Altitameare more than 2000-8000 times sweetening power as compared to sucrose. Dipeptide based sweeteners: Aspartame. Protein based sweetener: Thaumatin I & II.

Saliva stimulating agents [65-66]:

These are used to increase the secretion of saliva so that the oral film disintegrate and dissolve faster in the oral cavity. The acids which are used in the preparation of food are generally used as saliva stimulators. These agents aroused alone or in combination between 2-6%w/w of the oral strip. Citric acid, maleic acid, lactic acid, ascorbic acid, tartaric acid is the saliva stimulating agents. Citric acid is the most preferred among them. The stimulation of salivation can be measured by comparing the amount of resting flow & stimulated flow at equal time under same condition.

Flavoring agent:

The perception of flavour varies from individual to individual ethnicity and personal liking. Any US-FDA approved flavour can be added to the formulation according to the choice of the individuals of different age groups. The flavours liking changes with the age as geriatric population like mint or orange flavour while young generation like fruit, raspberry, strawberry flavour. Flavoring agent should be compatible with the drug and other excipients. Flavoring agents are selected depending on their flavour imparting capacity in first few seconds and its aftertaste. Upto 10% of the flavouring agent can be added to the oral strip formulation.

Colouring agents:

Colouring agents are selected according to the flavour. FD&C approved Colouringagents are incorporated in the oral film.

Method of Preparation:

Orally fast dissolving film can be prepared by different methods [67-89]:

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

Generally Solvent casting method is mostly preferred for the manufacture of fast dissolving film:

Solvent Casting Method:

This is the most preferred method to manufacture fast dissolving film. In this method firstly water soluble ingredients are mixed in water to form viscous solution. API and remaining ingredients are dissolved in smaller amount of solution and combined with bulk by using high shear processor. Vacuum is used to remove their entrapped. The solution formed is then cast as film and pour the solution in a glass mould and allow the solution to dry in an oven at 45-50°C which is then cut into pieces of the desired size.

Semisolid Casting:

This method is preferred when acid insoluble polymers are used in the preparation of oral fast dissolving film. Firstly solution of water soluble polymers is prepared. The solution is added to a solution of acid insoluble polymer. Plasticizer is added in the appropriate amount so that a gel mass is formed. The gel mass formed is then casted into the films or ribbons by using heat controlled drums. Acid insoluble polymers used to prepare films include: cellulose acetate

phthalate, cellulose acetate butyrate. The thickness of the film is about 0.015-0.05 inches. Acid insoluble polymer and film forming polymer are used in the ratio of 1:4.

Hot melt extrusion:

In this method the polymers which have low molecular weight and low viscosity are preferred. Drug is mixed with the carrier the solid form so that granular material is formed. These granules are then dried and then introduced into the extruder. The speed of the screw should be around 15rpm so that the granules reside inside the extruder for about 3-4min. The processing temperatures should be 80°C (zone1), 115°C (zone 2),100°C (zone 3), and 65°C (zone 4). The extrudate (T=65°C) then pressed into a cylindrical calendar to obtain a film.

Solid dispersion extrusion:

In this method immiscible components are taken they are then extruding with drugs. Solid dispersion is then prepared and by means of dies the solid dispersion misshaped into films.

Rolling method:

In this method firstly solution or suspension of drug is prepared which have certain rheological consideration. Either water or mixture of water and alcohol is mainly used as solvent. Suspension or solution containing drug is rolled on the carrier. Films are dried on the rollers and cut into desirable shapes and sizes.

Evaluation of The Oral Film [90-95].

- Mechanical properties

  - ✓ Thickness
  - ✓ Dryness/tacktest
  - ✓ Tensile strength
  - ✓ Percent elongation
  - ✓ Young's modulus
  - ✓ Tear resistance
  - ✓ Folding endurance
  - ✓ Organoleptic test
  - ✓ Swelling test
  - ✓ Surface pH test
  - ✓ Contact angle
  - ✓ Transparency
  - ✓ Assay/ content uniformity
  - ✓ Disintegration test
  - ✓ In-vitro dissolution test

Thickness:

A thickness of film should be measured with the help of micrometer screw gauge or calibrated digital vernier callipers. Film should be measured at five points i.e. from the centre and from all the four corners and then mean thickness is calculated. It is necessary to determine the uniformity of thickness as it is directly related to accuracy of dose in the film.

Dryness/ Tack test:

Dryness is the property to measure the solvent or water content present in the film whereas tack is the tenacity with which the film adheres to any piece of paper which is pressed into contact with the strip. Eight stages of film drying process have been recognized i.e. set-to-touch, dust free, tack-free, dry-to-touch, dry-hard, dry-through; dry-to-recoat & dry print free. Now instruments are also available to study.

Tensile strength:

It is the maximum stress applied to a point of a film at which the strip specimen breaks. It is calculated by applied load at rupture divided by the cross section area of the stripes given in the equation:

Tensile strength= Load at failure*100/ strip thickness* strip width

Percent Elongation:

When application of stress done, film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally elongation of film increases as the plasticizer content increases.

Percent elongation= L*100/L0

L = Increase in length of film
L0 = Initial length of film

Young's Modulus:

Young's modulus or elastic modulus is the measure of stiffness of film. It is expressed as the ratio of applied stress over straining the region of elastic deformation as follows:

Young’s Modulus= Slope*100/ Film thickness* crosshead speed

Brittle and Hard film demonstrates a high tensile strength and Young's modulus with small elongation.

Tear Resistance:

The maximum stress or force (that is generally found near the onset of tearing) required tearing the film is recorded as the tear resistance value in Newton (or pounds -force).

Folding Endurance:

Folding endurance is determined by repeated folding of the film at the same place till the fill breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Organoleptic Evaluation:

This is essential step in case of most oral formulation due to more residence time in the oral cavity. The product should possess the necessary features of sweetness and flavour which is acceptable to large mass of population. Special controlled human taste panels are used for the psychophysical evaluation of the product . In-vitro methods for utilization of taste sensors, specially designed apparatus and release of drug by Modified pharmacopoeial methods are being used for this purpose. Experiments using electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste masking formulation.

Swelling Test:

Simulated saliva solution issued to conduct the swelling property study. Firstly weigh all the samples of film and placed on the reweighed stainless steel wire mesh. 15ml of the saliva solution is added in the plastic container and the mesh containing film sample is submerged into it. Increase in weight of film was observed until a constant weight was observed.

The degree of swelling can be calculated using parameters: wt – wo/wo

wt = weight of film at time t
wo= weight of film at time zero

Surface pH Test:

Surface pH of the film was determined by placing the film on the surface of 1.5%w/v agar gel followed by placing pH paper (pH range1-11) on films. The change in the colour of pH paper was observed and reported.

Contact Angle:

Contact angle are measured by Goniometer (AB Lorentz and wettre, Germany) at room temperature. Take a dry film and place a drop of distilled water on the surface of the dry film.

Images of water droplet were recorded with in 10 sec of deposition by means of digital camera. The contact angle was measured on both side of drop and average is taken.

Transparency:

The transparency of the films can be determined using a simple UVspectrophotometer. Cut the film in the rectangular shape and placed inside the spectrophotometer cell. Determine the transparency of the film at 600nm.

The film Transparency was calculated as follows:

$$\text{Transparency} = (\log T600)/b = -\epsilon C$$

Where, T600= transmittance at 600nm
b= film thickness (mm)
C= concentration

Assay/ Content Uniformity:

This is determinedly any standard assay method described for the particular API in any of the standard pharmacopoeia. Determination of content uniformity is done by estimating the API content in individual strip. Limit regarding to content uniformity is 85-115%.

Disintegration Test:

The disintegration time limit is 90sec or less. Although no official guideline is available for oral strips. Pharmacopoeia disintegrating test apparatus may be used for the study. Typical disintegration time for oral strip is 5-30sec.

In-vitro Dissolution test:

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The media of dissolution will be selected as per the sink conditions and highest dose of the API. Most of the 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.

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Table 2: Generalized details of different ingredients of oral Film [96]

Drug(API)	5-30%
Water soluble polymer	45%
Plasticizer	0-20%
Saliva stimulating agent	2-6%
Surfactant	Q.S
Sweetening Agent	3-6%
Flavours, Colours, Fillers	Q.S

Table 3: Polymers available for preparation of ODF

S. no	Polymer Example	Reference
1. Natural Polymers	Pullulan, Starch, Gelatin, Pectin, Sodium alginate, Maltodextrins, Polymerized Rosin	[97]
2. Synthetic Polymers	Hydroxypropyl methyl cellulose, Sodium Carboxy methyl cellulose, Hydroxy propyl cellulose , Poly ethylene oxide, , Poly vinyl ethylene oxide, Hydroxy propyl cellulose, Poly vinyl pyrrolidone, Poly vinyl alcohol	[97]

Table 4: Patent reviews on ODF

Sr. no	Drug category	Polymer used	References
1	Antitussive and mucosa coating agent	Pullulan	[98]
2	Nutrients/flavours	Gelatin	[99]
3	Erectile dysfunction(Silendafil, Tadalefil, Vardenafil)	Plasdone, HPMC E-15 HPMC E4, HPMC E5 Maltodextrin	[100]
4	. Antimicrobial agents	. Antimicrobial agents	[101]
5	Dextromethorphan	Pullulan [	[102]
6	Menthol/Melatonin	PVA/HPMC	[103]
7	Vitamins	Pullulan	[104]
8	Nicotine	HPMC	[105]
9	Flavored	Maltodextrin, HPC	[106]
10	Breath freshening agents, flavors	Maltodextrin	[107]

11	Loratadine	PEO	[108]
12	Breath freshening agents egflavors	Pectin	[109]
13	Aripiprazole	Maltodextrin	[110]
14	Active Pharmaceutical ingredient.	PVA-PEG graft copolymer Kollicoat IR	[111]
15	Dextromethorphan	Pullulan	[112]
16	Nicotine	Mixture of polyalkylene oxide (POLYOX N 80) and a cellulose polymer(Methocel E 50) (ratio 1:2 to 1:5)	[113]

Table 5: Marketed products of oral film.

Oral Film	Active Ingredient	Manufacturer	Category
Klonopin Wafers	Clonazepam	Solvay pharmaceuticals	Antianxiety
Listerine cool mint pocket packs	Cool Mint	Pfizer	Mouth freshener
Benadryl	Diphenhydramine HCl	Pfizer	Antiallergic
Chloraseptic	Menthol /Benzocaine	Prestige	Sore throat
Gas-X	Simethicone	Novartis	Anti Flatuating
Sudafed PE	Phenylephrine	Wolters Kluwer Health Inc.	Reliving Congestion
SupressR	Menthol	InnoZenR, Inc	Cough suppressants
Triaminic	Diphenhydramine HCl	Novartis	Anti allergic
Theraflu	Dextromethorphan HBR	Novartis	Cough suppressants

CONCLUSION

Fast dissolving oral films have several advantages over the conventional dosage forms. That's why they are of having great importance during the emergency cases such as allergic reactions and asthmatic attacks whenever immediate onset of action is desired.

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