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Recent Trends in the Development of Oral dissolving Film

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Abstract: Oral dissolving films 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. This it offers shortening onset time, enhancing bioavailability and reducing the probability of first pass side effect. The current review focuses on the recent development in the oral dissolving film and discusses about its technique for preparation of film as well its evaluation.
Key word: Oral dissolving film, Film forming polymer, Solvent casting technique, Buccal cavity.

INTRODUCTION

Some patients have difficulties in swallowing or chewing solid dosage which forms risk or fear of chocking so this is a major problem in the use of tablets. Oral dissolving film is a new drug delivery system for oral delivery of drug. Oral film a type of film which is used in acute condition such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, and Asthma etc. oral dissolving film has gained popularity due to its availability in various size and shape[1.] Oral dissolving films are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients absorption is possible through the oral mucosa and may improve bioavailability[2.]

The concept of oral dissolves film

- This delivery system consists of a thin film.
- After placing it on the top of the tongue, the film dissolves within seconds, promoting first pass metabolism as compared to tablet and other immediate release oral solid dosage forms, and may increase the bioavailability of drug [3.]
- FDF dissolves in the mouth like a cotton candy.

Advantages of oral dissolving film (ODF) over fast dissolving tablet (FDT)

- Accessibility of larger surface area that leads to quickly disintegrate and dissolution in the oral cavity within seconds [4].
- ODF is flexible so they are not as fragile and need not any kind of special package for protection during transportation and storage as compared to FDT.
- No need of water has led to better satisfactoriness amongst the dysphasic patients.
- No fear of chocking as compared to FDT.
- The large surface area available in the film dosage form allows rapid wettive by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and on increase the bioavailability [5].
- The dosage form can be consumed at any place and any time as per convenience of the individual.

- The first pass effect can be avoided, so a reduction in the dose which can lead to reduction in side effects associated with the molecule [6].
- Patients suffering from dysphagia, repeated emesis, hypertension, heart attack, asthma, motion sickness, paralysis and mental disorders prefer this dosage form as they are not capable to swallow large quantities of water.

FORMULATION FOR FILM

The area of drug loaded film should be between 1-20 cm^2 which depends on the amount of water-soluble polymers that are responsible for rapid disintegration.

Table shows: Composition of fast dissolving film [7]

S. No.	INGREDIENTS	AMOUNT (w/w)
1	Active pharmaceutical ingredients	5 to30%
2	Water soluble polymer	45%
3	Plasticizer	0 to20%
4	Saliva stimulating agent	2 to 6%
5	Surfactant	q.s.
6	Sweetening agent	3 to 6%
7	Flavors, colors ,fillers	q.s.

FILM FORMING POLYMERS

Water soluble polymers are used such as HPMC E-3, E-5 E-15, K-3., Methyl cellulose A-3, A-6 and A-6., Carboxymethylcellulose, pullulan, maltodextrin, hydroxypropylcellulose cekol 30, polyvinyl alcohol etc. for the preparation of the oral soluble film. They can be used individually as well as in combination, to impart the desired properties into the film.

Ideal property of the film forming polymer

- It should have good shelf life
- It should have good wetting property
- It shall have good spread ability property
- It should not aid in cause secondary infections in the oral mucosa/ dental region
- It should have a good mouth feel property
- Polymer employed should be non-toxic,non-irritant and devoid of leach able impurities.

PLASTICIZERS

It is an important ingredient in oral film because it imparts flexibility to the film by reducing its brittleness and improves the strip property for preparing the oral film. It also improves the flow of polymer and enhances the strength of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also solvent employed in the casting of the strip. Plasticizers are commonly used in the concentration of 0-20%w/w of dry polymer weight[8].

ACTIVE PHARMACEUTICAL INGREDIENT (API)

The oral fast dissolving film technologies have the prospective for delivery of variety of API. But as the size of the dosage form is limited, High dose molecule is difficult to be incorporated into the films. Only 5mg to 30mg of API can be incorporated into the film. Insoluble API is dispersed uniformly in the film. API s can also be added as milled, micronized and also in the form of nanocrystals or particles depending upon the ultimate release profile. Several APIs that can be potentially used for oral film technology are with bitter taste which makes the formulation unpleasant, especially for pediatric formulations. This leads to the very significance unit operation –taste masking, before incorporating the API in the oral dissolving film. Various methods can be used to improve the palatability of the formulation.

Simplest method

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

Barrier method

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

SALIVA STIMULATING AGENT

A saliva stimulating agent is used to increase the rate of production of saliva would aid in the more rapidly disintegration of fast dissolving film formation. Saliva stimulating agents are used alone as well as in combination between 2 to 6% w/w of the weight of the film [9].

SWEETENING AGENT

This is the most major part of the food product or in pharmaceutical dosage forms, proposed to be disintegrated or dissolved in the oral cavity. Natural as well as artificial sweetening agent is used to improve the palatability of the formulation. Sweetening agent generally used either alone or in combination between the concentrations of 3 to 6%w/w [10, 17].

FLAVORING AGENT

Selection of flavor is depending on which type of drug is to be incorporated in the formulation. The recognition of the oral disintegrating / dissolving formulation by an individual, depends on the initial flavor quality which is observed in the first few

seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min.

The amount of flavor required to mask the taste depends on the flavor type and its strength. Preferably up to 10%w/w flavors' are added in the formations [11].

SURFACTANT

Surfactant are used as a solublising or wetting dispersing agent so that the film is getting dissolved within seconds and release active agent immediately.

COLORING AGENT

FD&D approved coloring agent are used in the manufacturing of oral dissolving film. (Not exceeding concentration levels of 1%w/w)**.** For example: titanium dioxide.

GENERAL TECHNIQUE FOR PREPRATION FILM [2]

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

1. SOLVENT CASTING METHOD

In this method, water soluble polymer is completely dissolved in to form uniform clear viscous solution other ingredients including API are dissolved in a small portion of aqueous solvent by using a high shear processor. This viscous solution is degassed under the vacuum to remove the air bubbles. This bubble free solution is poured into a glass mold and kept in oven at 40 º-50 º C [12--13].

Table shows- Type of agents used for preparation of oral dissolving film.

Plasticizers	**Sweetening Agent**	**Flavorings Agent**	**Colorings agent**	**Saliva stimulating Agent**	**Surfactant**
Acetyl triethyl citrate	Mannitol; Sorbitol	Lemon	Natural Coloring agent	Citric acid	Polaxamer 407
PEG	Xylitol ; Polyols	peppermint	Titanium oxide	Lactic acid	Benzalkonism chloride
Propylene glycol	Aspartame	Cinnamon	Silicon dioxide	Malic acid	Benzthonium chloride
Sorbitol	Glycyrrhizin	Vanillin	Zinc oxide	Ascorbic acid	Tweens
Glycerin	Saccharin; Cyclamate	Menthol		Tartaric acid	Spans
Citrate ester	Malitol; Isomalt malitol	wintergreen		Sodium lauryl sulphate	
Triacetin	Acesulfame potassium	Orange			
Triethyl citrate	Dextrose; Fructose	Clove			

Table shows-Specification condition required by using solvent casting method

Specification condition required by using solvent casting method							
Mixing condition		Agitated emulsification Device		Vaccum Defoaming Device		Coating Appratus	
Temp	20-90ºc	Flow rate	80L/h	Flow rate	80L/h	Passage time	2-8 min
Agitating Time	40-120min	Agitating Time	15min			Drying temp	50-130ºC
Rotating speed	1000-2000 Rpm	Homogenizer Pressure	15min			Solution temp	40-90ºC

Table shows- Advantage and disadvantage solvent casting method

Advantage	Disadvantage
Great uniformity of thickness	Polymer must be soluble in a volatile solvent or water
Great clarity then Extrusion	Viscosity should be formed
More Flexibility	
Better physical properties	
Finished film thickness is typically12-100µm	

2. HOT MELT EXTRUSION

Hot melt extrusion process based on polymer with a high glass transition temperature such as PVP [14].

Table Shows-Solving Pharmaceutical Challenge

Problem	Solution by HME
Poor bioavailability due to poor API solubility	Enhance dissolution
Poor API stability during processing caused by hydrolysis	No hydrolytic stress
Poor taste of the API	Taste-masked dosage form
Manufacturing of film	Prepared various type of film such as oral film, buccal film etc

Table shows-Advantage and disadvantage of HME method [15]

Advantage	Disadvantage
Improved bioavailability of poorly soluble compounds	Thermal process (drug/polymer stability).
During Processing no required solvents and water	Flow properties of the polymer are necessary to processing.
Cost-effective process with reduced production time and reduced number of unit operations	Limited amount of available polymer
Sustained, modified and targeted release capability	Require high power input
Better content uniformity was obtained among granules of different size ranges.	The melt technique is that the process cannot be applied to heat-sensitive materials due to the elevated temperatures involved
Homogeneous distribution of fine particle occurs	Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
Superior stability at varying pH and moisture levels.	Higher-melting-point binders require high melting temperatures and can contribute to volatility problems especially for heat-labile materials.

3. ROLLING METHOD

In this method, suspension or solution containing drug is rolled on a carrier. The solution or suspension should have a specific rheological consideration. Solvent is mainly used water as well as a mixture of water and alcohol. Film is dried on the rollers and cut into desired shapes and sizes [33].

4. SOLID DISPERSION EXTRUSION

In solid dispersion extrusion method immiscible components is extrude with drugs and then solid dispersions are prepared. Finally the solid dispersions are shaped into films by means of dies [16].

5. SEMISOLID CASTING METHOD

In this method, first of all a solution of water soluble film forming polymer is prepared. Then resulting solution is added to a solution of acid insoluble polymer. Then approximate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted into the films or ribbon by using heat controlled drums. The thickness of film is about 0.015-0.05 inches. The ratio of the acid insoluble polymers to film forming polymer should be 1:4. [17]

REVIEW OF RESEARCH WORK

Seema S et al (2011) developed fast dissolving films of pullulan polymer. This film contained PEG, propylene glycol, glycerine as plasticizers. These Films prepared as solvent-casting method. Lower concentration of polymer and plasticizer showed optimum performances. Propylene glycol shows best results as compared to other plasticizers [8].

S. Raju et al (2011) developed Flash release oral films of metoclopramide hydrochloride. This film contained polymers as a HPMC-E6 and sodium CMC. Glycerol as a plasticizer, Sodium bicarbonate as a disintegrating agent, Citric acid as an anti oxidant and saliva stimulating agent, Tween-80 as surfactant and Saccharin sodium was as a sweetener. Formulation containing HPMC-E6 is released 99.40% of drug within 30 seconds [9].

Kiran K et al (2011) developed oral thin film of rizatriptan benzoate. This film contained polymer-HPMC E5LV; plasticizer-PEG 400; sweetener-aspartame and flavor-pineapple; saliva stimulating agent-citric acid. Disintegration time was found to be within 10 seconds [31].

Renuka M et al (2010) developed rapidly dissolving films of cetiriziene hydrochloride, useful for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic urticaria by using pullulan as a film forming agent. This film contained pullulan as a polymer; PEG400 as a plasticizer; aspartame, sucralose as a sweeteners, citric acid as a saliva stimulating agent and fruit flavors as flaving agents [18].

Koland M. et al (2010) developed fast dissolving sublingual film of ondansetrol hydrochloride useful as anti-emetic. This film contained PEG400 as a plasticizer; polyvinylalchol, polyvinylpyrrolidone, carbopol934p as a polymer in different ratio and mannitol or sodium saccharin as a sweeteners. The film as prepared by solvent casting method [19].

Mahesh A. et al (2010) developed fast dissolving film of levocetirizine di hydrochloride, useful for the treatment of acute allergic rhinitis and chronic urticaria. They used taste masked ability of cyclodextrin by using solvent casting technique for developing film. This film contains kollicoat IR as hydrophilic polymer; aspartame as a sweetener; pre-gelatinized as a disintegrate agent. Levocetirizine dihydrochloride was incorporated into this film by *in-situ* complex formation with hydroxyl propyl de ß-cyclodextrin [20].

Kulkarni A.S. et al (2010) developed oral fast dissolving strips by use of different polymer in the formulation by using Solvent casting technique. The different polymer was explored for the formulation of strip such as HPMC E-15, HPMC K4M, HPMC E-5, PVA, PVP, Gelatin, Eudragite RL 100 and Pullulan with different excipients such as carrageen, Guar gum, PEG 400, Glycerin. The result was found that Pullulan and HPMC E-15 were having desired film forming capacity [21].

Kunte S. et al (2010) developed verapamil fast dissolving strips allowing fast, reproducible drug dissolution in the oral cavity; thus bypassing first pass metabolism. The fast dissolving strips was prepared by solvent casting technique with the help of HPMC E6 and maltodextrin [22]. Disintegration time was found to be in the range of 20.4-28.6 sec. It was concluded that the fast dissolving strips of verapamil can be made by solvent casting technique with enhanced dissolution rate, taste masking, and hence better patient compliance and effective therapy.

Shimoda H. et al (2009) developed fast dissolving oral thin film that contained drug dexamethasone and base material microcrystalline cellulose, PEG 400. This has shown excellent uniformity and stability, when stored it 40º C and 75% humidity for up to 24 week. This film gets disintegrate within seconds after immersing it in distilled water [23].

Patel R. et al (2009) developed mouth dissolving thin film useful for the treatment of anti-emetic drug. These films contain ondansetron with low viscosity HPMC E15 and maltodextrin which are used as an excepient due to their excellent film forming property and palatable taste [24].

Nishimura M. et al (2009) developed oral disintegrating film for the treatment of anti-cancer agent or opioid analgesics. It contained prochloperazine using microcrystalline cellulose, polyethlene glycol and hydroxypropylmethyl cellulose as the base materials. The film showed an excellent stability at least for 8 week when stored at 40ºC with 75% humidity. The dissolution test revealed a rapid disintegration property, in which most of prochorperazine dissolved within 2 min after insertion into the medium [25].

Sumitha Ch. et al (2009**)** developed thin films of ondansetron HCL and taste masking was done by complexion. Ondansetron HCL was mixed with ion exchange resin (polacriline potassium), also has disintegrating property, in different ratios and sucralose was added as sweetening agent in very low concentrations. Films containing mannitol and sorbital in the ratio of 1:1 and 7% wt/wt PEO N-10 showed faster disintegration, within 12.5 seconds [26].

Cilurzo F. et al (2009) developed a fast dissolving film made of low dextrose equivalent maltodextrins (MDX) containing nicotine tartrate salt (NHT) [27]. Particular attention was given to the selection of the suitable taste-masking agent (TMA) The placebo and NHT loaded films was prepared by coating technology. The films disintegrated within 10 sec. The addition of NHT caused a significant decrease of ductility, expressed as elongation at break, and an increase of the modulus of elasticity that is an index of stiffness. Among the tasted TMA, the 'milk' flavor resulted particularly suitable to mask the taste of NHT.

Aditya D. et al (2008) developed fast dissolving films of triclosan useful for broad spectrum anti-microbial agent that exhibited activity against wide range of gram-positive and gram-negative bacteria, molds, yeast and even parasites which are responsible for malaria and toxoplasmosis [28]. This film contained Propylene glycol as a plasticizer; glycerin as humectants, polyhydric alcohol; aspartame as a sweetener. Film was prepared by solvent casting technique.

Mashru RC.et al (2005) developed fast-dissolving film of salbutamol sulphate, which can be useful in an acute attack of asthma. The film was prepared using a solvent evaporation technique and is taken through the sublingual route. The film contains polyvinyl alcohol as a polymer, glycerol as a plasticizer, and mannitol as filler. The result was found that the optimum values of the responses for fast release film could be obtained at medium levels of polyvinyl alcohol and glycerol with high level of mannitol [36].

Cilurzo F. et al (2005) studied the feasibility of a fast dissolving film containing piroxicam . Maltodextrin used as a plasticizer and glycerin was used as a carrier. The film was produced by hot-melt extrusion technology. The films administered to five healthy volunteers disintegrated within 1 min and had a good compliance [29].

EVALUATION OF ORAL FILM

Drug content uniformity

$25cm^2$ area of the film is transferred into a flask containing 100 ml of distill water. The flask is shaken 3 to 4 hours in a mechanical shaker. The solution is filtered and after suitable dilution the absorption is measured against the blank solution. The drug content is calculated. Limit of content uniformity is 85–115 percent (The uniformity of dosage units should be acceptable according to JP15 or USP27).

Film thickness

A thickness of the film should be calculated by using micrometer screw gauge .Film should be measured at five positions i.e. central and the four corners and the mean thickness are calculated. This test should be performed on six films of each formulation maximum variation in the thickness of the films should be lessthan 5% and mean±S.D calculated. The thickness of the films maximum of less than 5% .[30]

Surface pH

The surface pH of the oral dissolving film is calculated in order to investigate the risk of any side effects *in vivo*. Since acidic or alkaline pH may cause irritation to the oral mucosa, it is determined to maintain the surface pH as close to neutral as possible [33]. A combined pH electrode is used for this purpose. The oral film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed in six films of each formulation and mean±S.D calculated [9].

Folding endurance

It is measured manually for the prepared oral film. A film was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test should be performed on six films of each formulation and mean±S.D calculated [9].

Tensile strength [32]

It is calculated by using a small oral film fixed to assembly. The weight required to break the film is noted and simultaneously film elongation is measured with the help of pointer mounted on the assembly. Where W, T and L are width, thickness, and length of the strip, and ΔL is the elongation at break.

Tensile strength =Break force /WT $(1+ \Delta L/L)$

Percentage elongation

It was calculated by the distance travelled by pointer before the break of the film on the graph paper [30].

% Elongation =

(increase in length/original length)X 100

Disintegration/dissolving time
It is calculated manually by dipping the film in 10 ml of water in a beaker with gently shaking when the film was dissolved, time was noted [32]. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral film. Disintegration time will vary depending on the formulation but typically the disintegration range from 4 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films [5].

***In-vitro* drug release**
A dissolution study of films is performed by USP XXIII type II apparatus in 6.8 phosphate buffer (300ml). The temperature (37±0.5°C) and the rotation speed was 50 rpm. The samples are withdrawn at time intervals and analyzed spectrophotometrically [32].

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

Young's modulus
Young's modulus is the measure of the stiffness of the film. It is represented as the ratio of applied stress above strain in the region of elastic deformation as follows-

Young's modulus= (Force at corresponding strain/cross section area)×1/(corresponding strain)

Swelling property
Film swelling studies are conducted using the simulated saliva solution. Each film sample is weighed and placed in a previewed stainless steel wire mesh. The mesh containing the film sample is submerged into a 15ml medium in a plastic container. An increase in the weight of the film is calculated at preset time intervals until a constant weight is observed [5].
The degree of swelling is calculated by using parameters
$\alpha = WT / Wo$
WT is weight of film at time T
T and Wo is weight of film at time zero.

Organoleptic evaluation
For sacrificial 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 modifying pharmacopoeia 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 [6].

CONCLUSION

The oral dissolving films are getting importance in pharmaceutical field. They offer many advantage over other dosage forms as well as they offer easy production and evaluation technique. This review is an effort to combine the knowledge available on oral dissolving films. A lot of research work is going on and will be started in near future on oral dissolving film.

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