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ORAL DISSOLVING FILMS: A REVIEW

Himani and Garg Rajeev
Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy,
Bela (Ropar)

Abstract:
Over the past few decades, tendency towards innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. OFDFs are gaining the interest of large number of pharmaceutical industries.In the late 1970s, rapid disintegrating drug delivery system was developed as an alternative to capsules, tablets and syrups for geriatric and pediatric patients having problems in swallowing.Oral disintegrating film or strips containing water dissolving polymer retain the dosage form to be quickly hydrated by saliva, adhere to mucosa, and disintegrate within a few seconds, dissolve and releases medication for oral mucosal absorption when placed in mouth. Oral film technology is the alternative route with first pass metabolism .The present review provides an account of various formulation considerations, method of preparation and quality control of the OFDFs.

Keywords: *Fast dissolving films, Fast disintegration ,Oral strips ,Thickness ,Tensile strength.*

Corresponding author:
Himani,
Amar Shaheed Baba Ajit Singh Jujhar Singh
Memorial College of Pharmacy,
Bela (Ropar)

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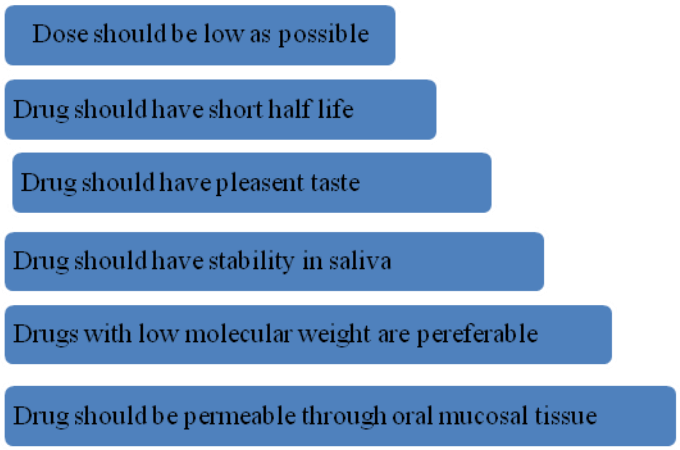
INTRODUCTION:

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking[1-4]. In this condition, oral fast dissolving drug delivery system is such a peculiar approach to increase patient compliance by its quality of rapid disintegration and self administration without swallowing and chewing[5]. Oral dissolving film or strip can be defined as, "A kind of formulation which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva." The films are designed to dissolve upon contact with a wet surface, such as tongue, within few seconds, meaning the consumer can take the product without need for additional liquid. The sublingual mucosa having thin membrane and large veins is more permeable. It gives instantaneous bioavailability of drugs due to rapid blood flow. Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption

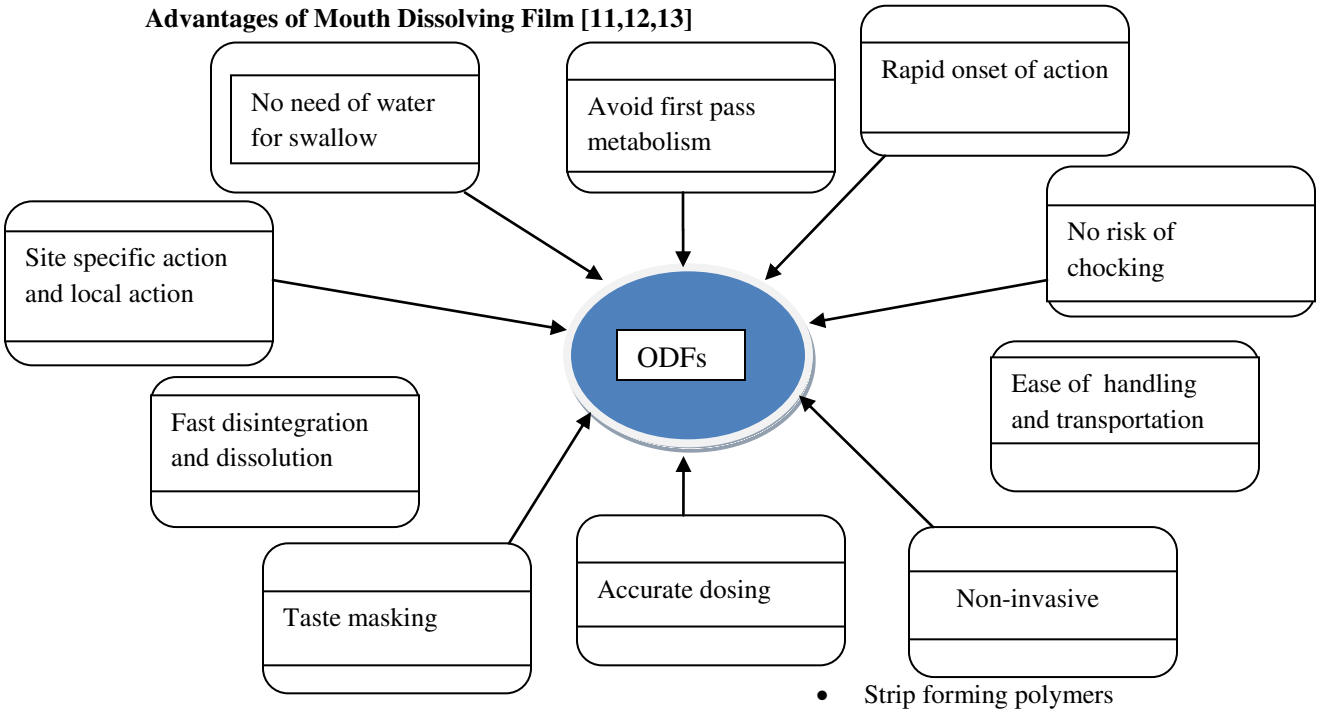
Special features of mouth dissolving films[6,7]

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release

Ideal characteristics of a drug to be selected [8,9,10]



Advantages of Mouth Dissolving Film [11,12,13]



Disadvantages of oral disintegration film(14)

• Restriction of eating and drinking
• Not suitable for drugs which are unstable at buccal pH.
• Dose uniformity is a technical challenge.
• Packing requires special equipment So, difficult to pack.
• Only drugs with small dose can be administered.

Applications of oral films in drug delivery (15,16)

- The oral films are ideal in the delivery of active agents like analgesic or antimicrobial ingredients for the care of wound and other applications.
- Oral drug delivery by mucosal , sublingual and buccal become preferable for therapies in which immediate absorption is required including those used to manage pain, allergies, CNS disorders and sleep problems.
- water soluble molecules of different molecular weights are incorporated in film and the solubility of poorly soluble drugs are enhanced by using hydrophillic polymers
- Dissolution of oral films could be initiated by the pH or enzymatic secretion of GIT and are used to treat gastrointestinal disorders
- Used to avoid bad mouth order by incorporating mouth freshing flavours.
- Oral films loaded with sensitive reagent to allow controlled release to biological fluid for separating multiple reagents to allow a timed reaction within diagnostic device.

Oral film formulation components-:

- Active pharmaceutical ingredients
- Strip forming polymers
- Plasticizers
- Sweetening agents
- Saliva stimulating agents
- Flavoring agents
- Coloring agents
- Stabilizing and thickening agents

Active pharmaceutical ingredients (17,18,19)- The main disadvantage of oral film is that the size of the dosage form due to which high dose could not be loaded. We incorporate 5% w/w to 30% w/w of active pharmaceutical ingredients. APIs can be milled, micronized or loaded in the form of nanocrystals or particles depending upon the ultimate release profile desired. For bitter drugs taste required to be masked before incorporating APIs in the Oral strips.To enhance the taste different techniques are used but the simplest method includes mixing and co-processing of bitter testing API with excipient with good pleasant taste called as obscuration technique. The selection of API depends on the potency of API, dose as well as therapeutic efficacy. Most suitable API for ODF includes anti-allergic,anti histammic, anti Parkinson and analgesic drugs.

Table 1: The drugs which have incorporated via orally fast dissolving films are mentioned below

Drug	Action	Dose(mg)
Salbutamol	Anti asthmatic	4
Levocetrizine	Anti histaminic	75
Chlorohexidine	Antiseptic	12

Strip forming polymers (20,21,22) - : Strip forming polymer is the most essential and major component of the oral films. Various types of polymers are used in the preparation of oral films. Polymers can be used alone or in combination to get the required film properties for the preparation of oral film and to prevent damage during handling and transportation. At least 45% w/w of polymers should present because strip forming polymer is the important constituent of the oral films. The polymer should exhibit sufficient peel, shear and tensile strengths .The polymers can be used alone or in combination to improve hydrophilicity, flexibility, mouthfeel and solubility characteristics of fast dissolving films. The stiffness of the strip depends on the type of polymer and the amount of polymer in the formulation. Since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity, the water soluble. In order to prepare a thin film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive and excellent film forming capacity.

- **Ideal properties of the polymer(23)-**
  - Inexpensive and easily available.
  - Non-bitter in taste or should be tasteless.
  - Long shelf life.
  - Non-toxic.
  - Chemically inert.
  - It should not contain impurities.

Table2:Polymers used in oral dissolving films(24)

Group	Class	Example
Natural	Carbohydrates	• Pullulan, Pectin, Sodiumalginate, Sodium starch glycolate, Maltodextrin.
	Proteins	• Gelatin
	Resins	• Polymerized rosin
Synthetic	Cellulose derivatives	• Methylcellulose(A3, A6,A15),Hdroxypropyl cellulose(E3,E5,E15, K3,K15),Carboxy - methyl cellulose, Sodium carboxy methyl cellulose
	Vinyl polymer	• Polyvinyl pyrrolidine , Pol-yethylene oxide
	Acrylic polymer	• Eudragit(RD-100,RL-100)

Plasticizer (25,26,27)-The mechanical properties such as elongation and tensile strength to the films have been improved by addition of plasticizer. Plasticizer helps to reduces the brittleness of the strip and improve its flexibility. Variation in their concentration may affect the tensile strength and elongation of the strips .Plasticizer used in the formulation should be compatible with the type of polymer used as it improves flow of the polymer and reduces the glass transition temperature. Use of inappropriate plasticizer may result in cracking, splitting and peeling of the strip. Plasticizer used in the formulation should be compatible with the type of solvent employed in the casting of film. The commonly used plasticizers are 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.

Sweetening agents (28,29)-Sweeteners are used to improve the taste of films. Sweeteners have very important part of the formulation intended to be disintegrated in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 %w/w in combination with isomalt as they additionaly provide good mouth feel and cooling sensation. Natural as well as artificial sweeteners are used to improve the taste as well as intended to be dissolve and disintegrate in the oral cavity. The classical source of sugar is sucrose, fructose, glucose and dextrose. Saccharine, Sucralose and aspartame are fall in to the artificial sweetener category.

Stimulating agents (30)-Production of saliva helps in faster disintegration of the film. So, the saliva stimulating agents are used to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations .Some commonly used saliva stimulating agents are tartaric acid, malic acid, citric acid , ascorbic acid

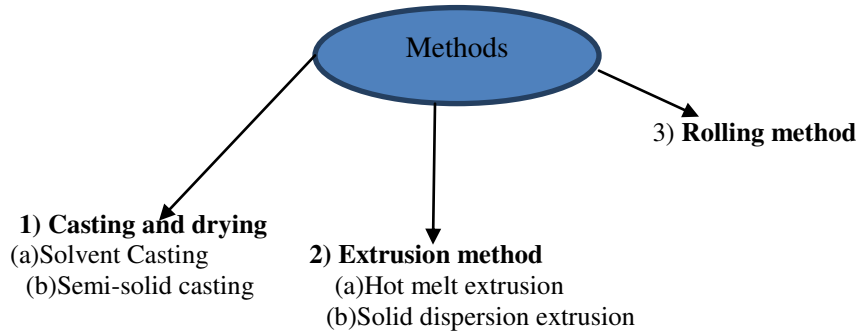
Flavouring agent(45,46)-Flavours are used to mask the bitter taste of selected drug. Amount of flavour depends upon its strength and nature. Any US-FDA approved flavour can be used such as sweet ,sour or mint flavour .These agents can be selected from the synthetic flavor oils, oleo resins. Extract derived from various parts of the plants like leaves, fruit and flowers. The amount of flavour to be used depends upon the type of flavour used. The age factor have important role in the taste. The young generation like fruit flavours while geriatric population like mint, cinnamon, clove etc.

Colouring agent (47,48)-Pigments are used as colouring agents. The purpose of colouring agent is to improve the appearance of the films. Only FD&C approved colours are used. Other colouring agents used in the formulation of oral films are EU colours , custom pantone matched colours ,natural colours. The colouring agent in oral films are used in concentration level of 1% w/w.

Stabilizing and thickening agent (31)-To improve the viscosity and consistency of formulation, the stabilizing and thickening agents are incorporated. Natural gum, like xanthan gum, carrageenan and cellulose derivative are loaded up to 5% w/w.

Methods for preparation of oral dissolving films-

Different methods for producing oral films are classified as follows**:**



(a)Solvent casting method (32,33)- In this solvent casting method, firstly water soluble polymers were dissolved in water.

Then the drug along with other excipients were dissolved in same solution and then mixed and stirred it for 2 to 2.5 hours on magnetic stirrer.

Then sonicate this solution for 1 hour for removing all bubbles.

Then cast the above solution in to the petri dish and then dried it at 50ºC for 24 hours.

Then removed the film from petridish carefully, checked for any imperfections and then cut into the required size to deliver the equivalent dose per strip.

Then the samples are stored in desiccator until further analysis.

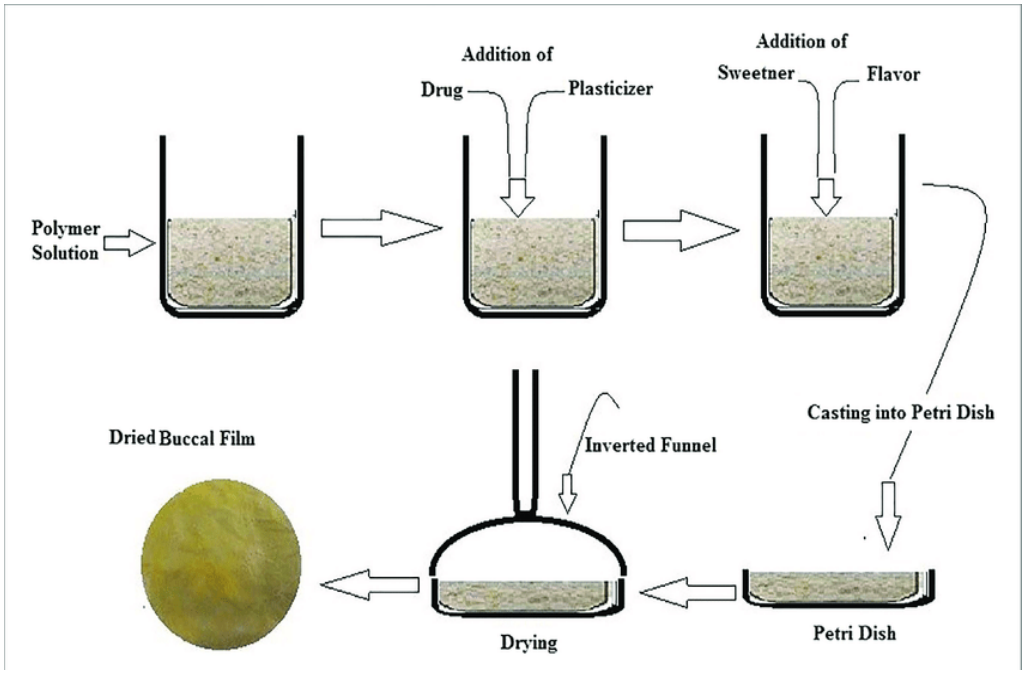


Fig1:Solvent casting process for the preparation of mucoadhesive buccal film.

Advantages-

- The thickness uniformity of the film and clearity is better than extrusion method.
- Films are free from defects and have fine gloss.

Disadvantages-

- Solution formed should be stable and have minimum or no solid content.
- The polymer used for preparation of the film must be soluble in a volatile solvent and water.

(b)Semi casting method (36)-

Firstly, a solution of water soluble film forming polymer is prepared in semi-solid casting method.

prepared solution is added to acid insoluble polymer like cellulose acetate butyrate, cellulose acetate phthalate etc.

Then add accurate amount of plasticizer to get gel mass.

Finally cast gel mass into films by using heat controlled drums.

On drying the thickness of the film is about 0.015-0.05g

Extrusion-

a) Hot melt extrusion (34,35)-This method involves shaping a polymer into a film by heating process rather than through the solvent casting method. solvent systems are not used in this process.

In this method firstly API and other ingredients are mixed in dry state which are subjected to heating process and then extruded out in molten state

↓

The molten mass thus formed is used to cast the film

↓

The films are further cooled and cut to the desired size.

Drying process and casting are two critical steps in this technique.

Advantages-

- Uniform dispersion of the fine particles because of intense mixing and agitation
- No need of solvent or water.

Disadvantages-

- Disadvantage of this technique is that degradation of thermolabile APIs due the use of high temperature.
- Polymer stability problem, limited no of available polymers.

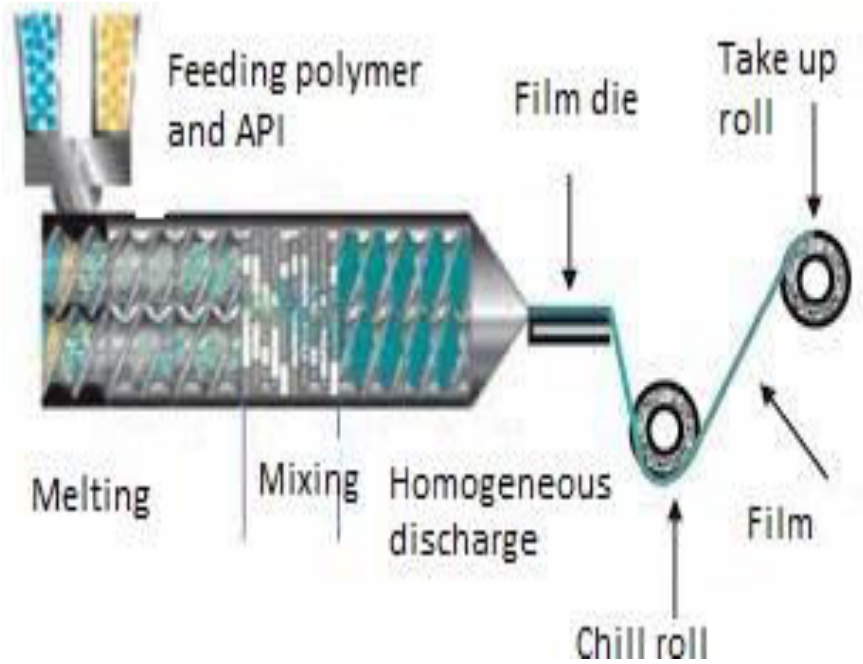


Fig2:Hot melt extrusion technique

b)Solid dispersion extrusion(51)-The term solid dispersion refers to the dispersion of one or more APIs in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers using methods such as HME.

In this method firstly, immiscible components are extrude with drug

↓

Then solid dispersions are prepared

↓

Finally the solid dispersion are shaped into films by means of dies

Advantages-

- This mehod is used to improve dissolvability in water of a poorly water-soluble drug in pharmaceutical.
- By using this method crystalline structure of drug is reduced to amorphous form.

Disadvantages-

- Some times it is difficult to handle because of tackiness.
- Moisture and temperature have more of deteriorating effect on solid dispersion.
- During formulation sometimes it may form hard lump which is very difficult to break on large scale.

(c)Rolling method(40)-In rolling method firstly solution containing drug with polymer is rolled on a carrier . solvents used are mainly water and mixture of water and alcohol.

↓

The film is dried on the rollers and cut into desired shapes and sizes**.**

Advantages-

- Better surface finish obtained.
- No heating required.
- Improved strength properties.

Disadvantage-

- Heavier and more powerful equipment requirred.
- May produce undesireable residual stresses.

Evaluation of oral dissolving film-

Mechanical properties-

- Thickness
- Tensile strength
- Percent elongation
- Youngs modulus
- Tear resistance
- Folding endurance

Physical properties

- Uniformity of weight
- In vitro dispersion test
- Dissolution test
- Stability testing
- Stability testing
- Drug content
- Surface PH test
- Swelling properties
- Organoleptic properties
- Contact angle
- **Mechanical properties**

- **Thickness(39)**-The thickness of the film can be measured by micrometer screw gauge at different 5 locations.This is helpful in determination of uniformity in the thickness of the film and this is directly related to the accuracy of dose in the film.
- **Weight variation(49)** - Individual films were weighed and the average weights were calculated. Then the average weight of the films is subtracted from the individual weight of the films. A large variation in weight indicates the inefficiency of the method employed and also due to non‐ uniform drug content in films.
- **Tensile strength(50)**- It is the maximum stress applied to a point at which strip specimen break. It is calculated by following formula:

  [Tensile strength] = Load at Failure× 100 / Strip thickness × strip width
- **Percent elongation(53)-**When stress is applied to the film, it stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

  % Elongation = Increase in length ×100/original length
- **Young's modulus (52)-** Elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as the formula is given following.

Yong's modulus

$$= \frac{Force\ at\ corresponding\ strain}{Cross\ sectional\ area} \times \frac{1}{Corresponding\ Strain}$$

- **Tear resistance(52)-**Tear resistance is a complex function of ultimate resistance of oral film to rupture. Mostly loading weight 51 mm (2 in)/min is employed that is very low and is designed to measure the force to initiate tearing. The maximum stress or force required to tear the specimen is recorded as the tear resistance value in Newtons.
- **Folding edurance(38)-**It gives indication about the brittleness of the films.It is determined by folding it repeatedly at the same place till the strip breaks**.**The number of times the film is folded without breaking is recorded as the folding endurance value

Physical parameters-

- **Uniformity of weight**- Each film was weighed individually on analytical balance and average weight of 3 films was taken. A large difference in weight indicates the unequal distribution of drug in the film**.**
- **In vitro dispersion test-**This method was also known as petridish method. A film was dropped in culture dish having diameter of 8cm,containing 10mL of simulated salivary fluid.The mean in vitro dispersion time of 6 films was determined.
- **Dissolution test(41)-**For dissolution testing the standard basket and paddle appratus described in official books can be used.It is carried out in simulated saliva appratus of 900ml of pH 6.8 phosphate buffer.The temperature of the appratus is maintained at 37±0.5.Samples are withdrawn at regular interval and analysed by UV-Visible spectroscopy. Paddle apparatus sometimes cause problem in dissolution test because of tendency of strip to float on dissolution medium.
- **Stability testing-**Accelerated stability study is carried out under common stress conditions like temperature, humidity and light. A piece of film was stored in an aluminium package at 25 with 50-60% humidity or at 40 at 75% humidity for 4-24 weeks ,then the content of drug was determined**.**
- **Drug content-**This test is necessary to check the uniformity of drug content in oral dissolving films**.**The estimation of drug content was made by random sampling of all batches.The oral film was dissolved in phosphate buffer and resulted solution was filtered and this filtered solution was injected into HPLC.Estimation was made as a mean of three determinations.
- **Surface PH test(42,43)-**Surface pH of the film can be 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. The change in the color of pH paper is observed.
- **Swelling properties**-It is determined by weighing each film sample and placing it in pre-weighed stainless steel wire mesh. The mesh containing film is submerged into 15 ml medium in a plastic container. Increase in the weight of film is determined at different time interval until a constant weight is observed. The degree of swelling was calculated by using following equation**:**

  α wt – wo/w

  Where: wt= Weight of film at time t

  wo= Weight of film at time zero
- **Organoleptic properties-**As we know the oral dissolving films intended to disintegrate rapidly in oral cavity so it is very important to focus on its organoleptic properties. Mostly peoples accept the products that possess features of sweetness and flavour. Special controlled human taste panels are used for its psychophysical evaluation. For this purpose, in-vitro methods of utilizing taste sensors, specially de-signed apparatus and drug release by modified pharmacopoeial methods are used. To differentiate between sweetness level in taste making formulation, experiments by using electronic tongue measurements were performed.
- **Contact angle(54)**-Contact angle of a film is usually measured at room temperature with the help of a device known as goniometer. On the dry film surface, a drop of double distilled water is placed. Water droplet images are recorded within 10 s after the placement of drop with the help of a digital camera. These digital pictures are analyzed by using image 1.28 V software for determining contact angle .Contact angle is measured on both sides of droplets and mean is calculated. Contact angle is determined at least five times at different positions to have a clear idea about the nature of film.

Marketed formulation-

Table3:Marketed products of oral films.

Product category	Ingredients	Indication\Application
1.Bio films		
Vitamin and food supplements	Various vitamins,minerals and supplements.	It is used for those patients who don't pop up tablets or soluble supplements.
Energy boosters	Caffeine,green tea extract and guarana. Fruit acid extract.	The product maintains the energy level.
Breath freshner strip	It contains mint flavor and anti-bacterial agent,cetylpyridinium chloride.	It is used in the dry mouth as a side effect of the other medication.
2.Bio delivery sciences Internationl		
Onsolis	Fentanyl/buccal soluble film	Pain in opioid tolerant patients.
BEMA buprenorphine	Buprenorphine	Therapeutic alternative for patient with in complete pain relief or those enable to tolerate.
3.Innozen inc		
Suppress cough strip with menthol	Ascorbic acid,aspartame,Sorbitol,spices,menthol,glycerin.	Suppresses cough.
Chloraseptic relief strip	Polyethyleneoxide,Benzocaine3mg,BHT, cornstarch,erythritol,FD&CRed40,hydroxypropyl methylcellulose mallic acid,menthol monoamonium glycyrrhizinate,cherry flavor,polyethyleneoxide,sucralose.	Occasional minor irritation,pain,sore throat and sore mouth.
4.Hughes Medical corporation		
Folic acid	1m-5mg	Needed for formation of healty red blood cells and used in anemia.
Diphenhydraine Hcl.	2.5mg-5mg	Antihistamine.

CONCLUSION:

From above,this can be concluded that oral films are considered as a most promising and efficaceous drug delivery system because of their rapid disintegration. Fast dissolving films have proved to be an innovative drug delivery system for all groups of population . They have improved acceptance and patient compliance with no risk of choking associated with better safety and efficacy in comparison with conventional dosage forms. The main idea behind formulation of ODFs was to cope with the difficulty in swallowing conventional oral dosage forms among pediatric, geriatric and psychiatric patients with dysphagia. ODF's are useful in cases where a rapid onset of action required such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma. Presently, ODFs are widely available for hypertension, acidity, allergy, pain etc reflecting their importance. Major advantages of such dosage form are their administration without use of water fulfilling the need of target population seeking convenience in drug administration along with bypassing the hepatic metabolism, consequently, leading to improved therapeutic response OFDFs are also having great potential of delivering the medicinal agent systemically as well locally and have several advantages over many dosage forms.Oral thin films are used as a good tool to increase the life cycle of the existing product by getting patent of same product as fast dissolving films.

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