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REVIEW ON MOUTH DISSOLVING 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 pediatric and geriatric patients who experience difficulties swallowing traditional oral solid- dosage forms. Fast dissolving films have become a novel approach to oral drug delivery system as it provides convenience and ease of use over other dosage forms such as orally disintegrating tablets, buccal tablets and sublingual tablets, so mouth dissolving films are gaining the interest of large number of pharmaceutical industries. Buccal drug delivery has lately become an important route of drug administration. But many of the patients (pediatric and geriatric) are unwilling to take solid preparations due to fear of choking. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Fast dissolving oral drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer, better patient compliance, rapid drug absorption and sudden-onset of drug action with instant bioavailability is possible. Formulation of mouth dissolving films involves both the visual and performance characteristics as plasticized hydrocolloids, API taste masking agents are being laminated by solvent casting and semisolid casting method. Solvent casting method being the most preferred method over other methods because it offers great uniformity of thickness and films prepared having fine glossy look and better physical properties. Mouth dissolving films are evaluated for its various parameters like thickness, physical property like folding endurance, disintegration and dissolution time. Present review provides an account of various formulation methods and their evaluation used in film formulations and applications of mouth dissolving films.

KEYWORDS: Mouth dissolving films, polymer, plasticizer, solvent casting, Buccal drug delivery, Formulation, Evaluation.

INTRODUCTION

Among the various routes, oral administration is the most preferred route. Most of the drugs are taken orally in the form of tablets, capsules, etc. by all patients including adult, pediatric and geriatric patients. But these dosage forms have to face many problems such as-

- Need of water for their disintegration.
- Choking problems
- Poor patient compliance
- Unpleasant taste and odour
- Difficult to administer in children, aged people, mental patients, in unconscious states, etc.[2]

Fast dissolving oral film, a novel drug delivery system for the oral delivery of the drugs is an ultra-thin film prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity. It is an ultrathin strip (50-150 microns thick) of postage stamp size with an active agent and other excipients developed on the basis of transdermal patch technology. These evolved from the confectionery and oral care markets over past decade in the form of breath strips and became a novel and widely accepted dosage form by consumers for delivering vitamins and personal care products. These fast dissolving oral films have persistent to extend in sales and launched as patient compliant and convenient products effectively addressing issues for pharmaceuticals as well as nutraceuticals that have been traditionally administered as oral solid dosages. 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.[1] It then rapidly disintegrates in a matter of seconds and dissolves to release medication for oromucosal absorption. Today, fast dissolving oral films are a well proven and worldwide accepted technology for the systemic delivery of active pharmaceutical ingredients (APIs).

What is Mouth Dissolving Film

It is a film containing active ingredient that dissolves or disintegrates in the saliva remarkably fast, within a few seconds without the need for water or chewing. Some drugs are absorbed well from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In

such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage from.

Table 1: Advantages and disadvantages of MDFS.[7]

Advantages	Disadvantages
Rapid onset of action	Low dose required
Patient complaint	Added cost for taste masking of bitter drugs
Used without water	Dose uniformity is technical challenge
Accurate dosing	Hygroscopic in nature
Avoid first pass metabolism	Required special packing

Ideal Requirement for Mdfs

The ideal requirements for MDF are as follows:[3-7]

- ✓ MDF should be thin and flexible, but stable to guarantee a robust manufacturing and packaging process and ease of handling and administration.
- ✓ The films should be transportable, not tacky and keep a plane form without rolling up.
- ✓ They should provide an acceptable taste and a pleasant mouth-feel.
- ✓ Disintegration time should be as short as possible.
- ✓ They should exhibit low sensitivity to environmental conditions such as temperature and humidity.
- ✓ Size of a unit FDF should not be too large that it will affect the patient's compliance.
- ✓ Surface of the FDF should be smooth and uniform.
- ✓ They should remain physically and chemically stable throughout its shelf life.

Tabale 2: Percentage of various ingredients used in formulation of MDFs.[9]

Sr. No.	Ingredient	Amount (W/W)
1	Drug (API)	5-30%
2	Water Soluble Polymer	45%
3	Plasticizers	0-20%
4	Saliva Stimulating Agent	2-6%
5	Surfactant	q.s
6	Sweetning Agent	3-6%
7	Flavour Colour Filler	q.s

Tabale 3: Examples of excipients used in formulation of MDFs.[4]

Drug	Polymers	Plasticizers	Sweeteners
Nicotine	Pullulan	Glycerol	Dextrose
Nitroglycerine	Hydroxy Propyl Methyl Cellulose	Propylene glycol	Fructose
Zolmitriptan	Poly(acrylic acid) derivetives	Dimethyl phthalate	Glucose
Loratidine	Sodium Carboxy Methyl Cellulose	Dimethyl phthalate	Maltose
Loperamide	Hydroxy ethyl cellulose	Dibutyl phthalate	Xylitol
Famotidine	Hyaluronic acid	Tributyl citrate	Maltitol
Florazepam	Xanthan gum	Trietylcitrate	Mannitol
Acrivastne	Locust bean gum	Acetyl citrate	Sucralose
Dicyclomine	Guar gum	Triacetin	Aspartame
Omeprazole	Carragenan	Castor oil	Alitame
Cetrizine	Sodium alginate	Lanoline alcohol	Niotame

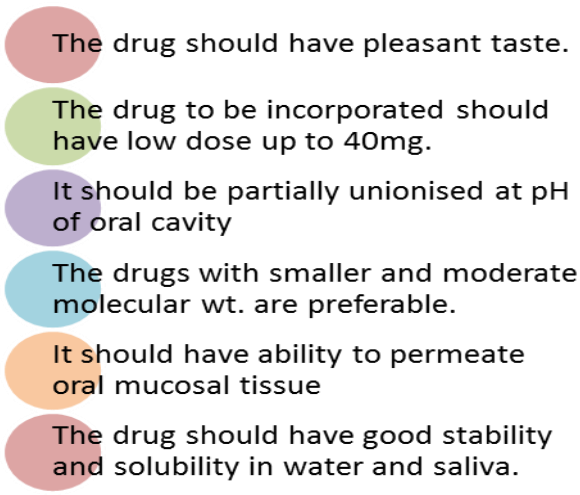
Formulation Aspects For Mouth Dissolving Films[11,12,13]

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

A) Drug Category (5-30%)

This technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose drugs are difficult to be incorporated in films. Less bitter, potent and highly lipophilic drug should be preferred for oral thin film as in case of fast dissolving tablets.

The ideal characteristics of a drug to be selected



Various categories of drugs such as antiemetic neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, antiparkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorents, etc.

Drug candidates suitable for MDF are shown in below

B) Film forming polymer (45%)

In order to prepare a film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer that is to be used should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. It should exhibit sufficient peel, shear and tensile strengths. It should be readily available and should not be very expensive. Some of the examples of suitable polymers that can be incorporated in the FDFs are HPMC, CMC, Gelatin, Pullulan, etc.[17]

Ideal properties of the polymers used in the oral film[11,12,13]

- Polymers should be non toxic, non- irritant and 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, shear and tensile strength
- It should not cause secondary infection in the oral cavity
- And should have sufficient shelf life.

C) Plasticizers (0-20%)

Plasticizer enhances mechanical properties such as tensile strength and elongation to the film by reducing the glass transition temperature of the polymer. It also reduces brittleness of the strip as a result improves its flexibility. Choice of plasticizer depends upon type of solvent used and its compatibility with the polymer. Some of the commonly employed plasticizers are phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin and glycerol. Improper use of plasticizer may lead to blooming, film cracking, splitting and peeling of the strip.[18,19,20,21]

D) Saliva stimulating agent (2-6%)

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving films. Generally acids which are used in the preparation of food can be used as salivary stimulants such as Citric acid, Malic acid, Lactic acid, Ascorbic acid and Tartaric acid.[23]

E) Surfactants (q.s)

Surfactants are used as wetting or solublising or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed are polaxamer 407, bezathonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is polaxamer 407.[22]

F) Sweetening agent (3-6%)

Sweeteners have become an important part of the formulation that disintegrate or dissolve in the oral cavity. Both natural as well as artificial sweeteners can be used in the formulation of these fast dissolving films. Polyhydric alcohols such as Sorbitol, Mannitol, and Isomalt can be used in combination as they provide good mouth feel and cooling sensation. However, use of natural sugars should be restricted in people who are on diet or in diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, Cyclamate and Aspartame are the artificial sweeteners.

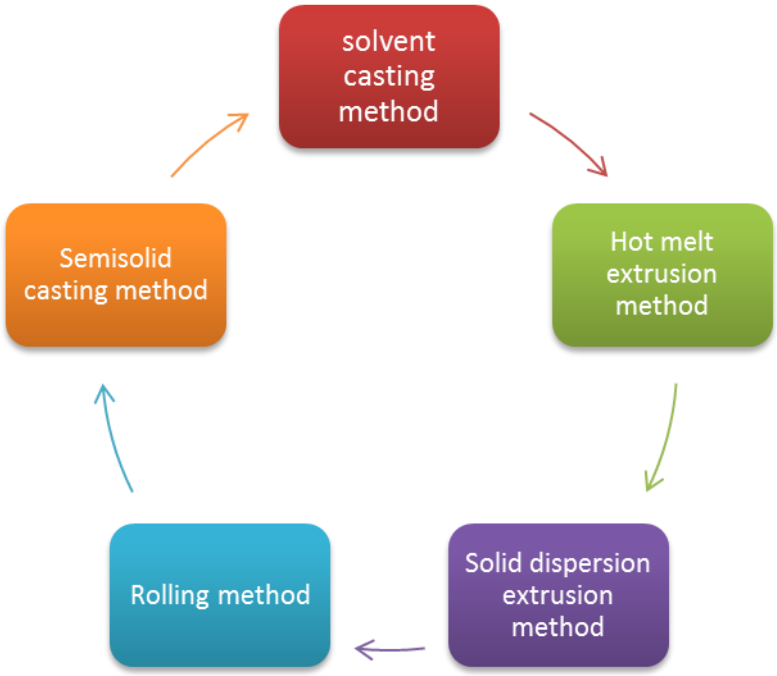
G) Colouring agents (q.s)

FD & C approved colouring agents are used for the fast dissolving films like Titanium dioxide.

H) Flavoring agents

Perception for the flavor changes from individual to individual depending on the ethnicity and liking. Flavoring agents can be selected from synthetic flavor oils, oleo resins extract derived from various parts of the plants like leaves, fruits and flowers. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

Manufacturing Methods[5]



1. Solvent casting method

In this method, firstly at the speed of 1,000 rpm the water soluble polymers are dissolved in water and heated up to 60oC. All the other excipients like colors, flavouring agent, sweetening agent, etc. are dissolved separately. Finally, both the solutions obtained are mixed thoroughly with stirring at the speed of 1,000 rpm. The API dissolved in suitable solvent is incorporated in the above obtained solution. By using vacuum the entrapped air is removed. The resulting solution is cast as a film and allowed to dry and then it is cut into pieces of the desired size.[5-10]

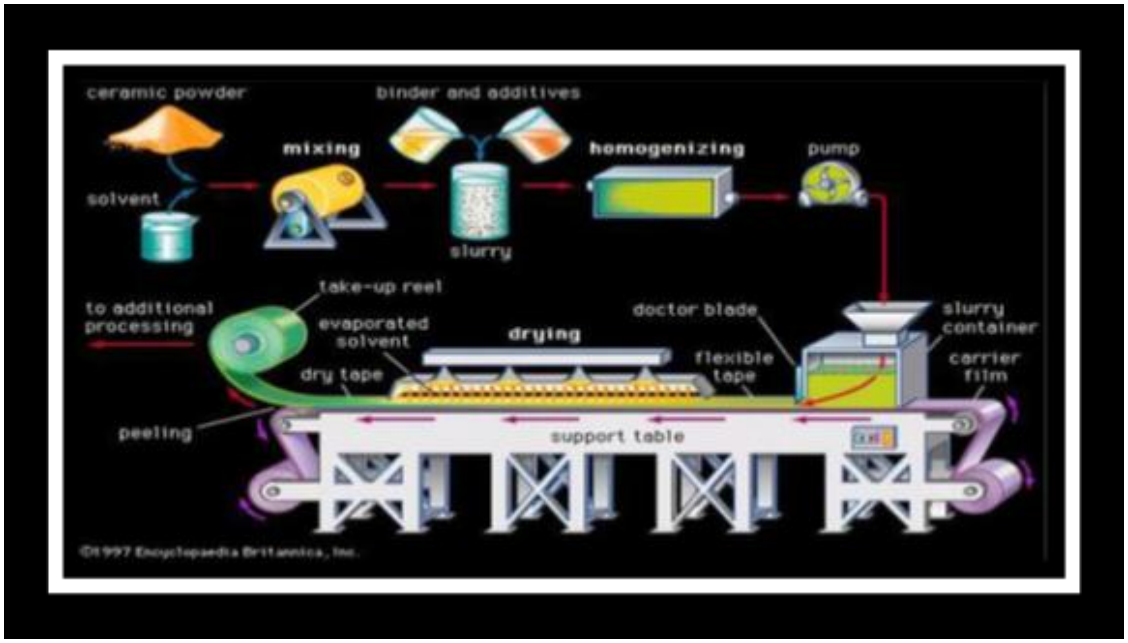


Fig. 1: Solvent casting method.

2. Hot Melt Extrusion[6]

In hot-melt extrusion, the dry ingredients for the film are heated and homogenized by the action of an extruder screw until they are molten and mixed. The melted material is forced through a flat extrusion die that presses the extrudate into the desired film shape. The thickness and strength of the film can further be affected by elongation rollers while the material is still hot and pliable. The extruded film is then cooled, cut and packaged.[6-16]

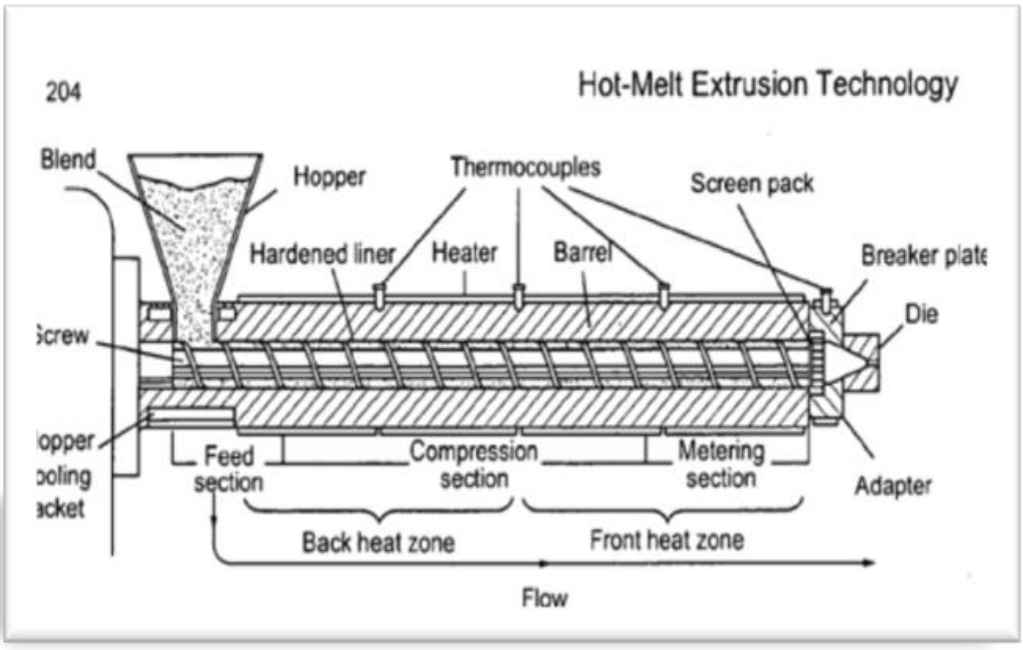


Fig. 2: Hot Melt Extrusion Method.

3. Solid dispersion extrusion method

Firstly solid dispersion is prepared by extruding immiscible components with drug and then shaped in to films by the means of dies.[15]

4. Rolling method

In rolling method a solution or suspension containing drug is rolled on a carrier. 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.[14]

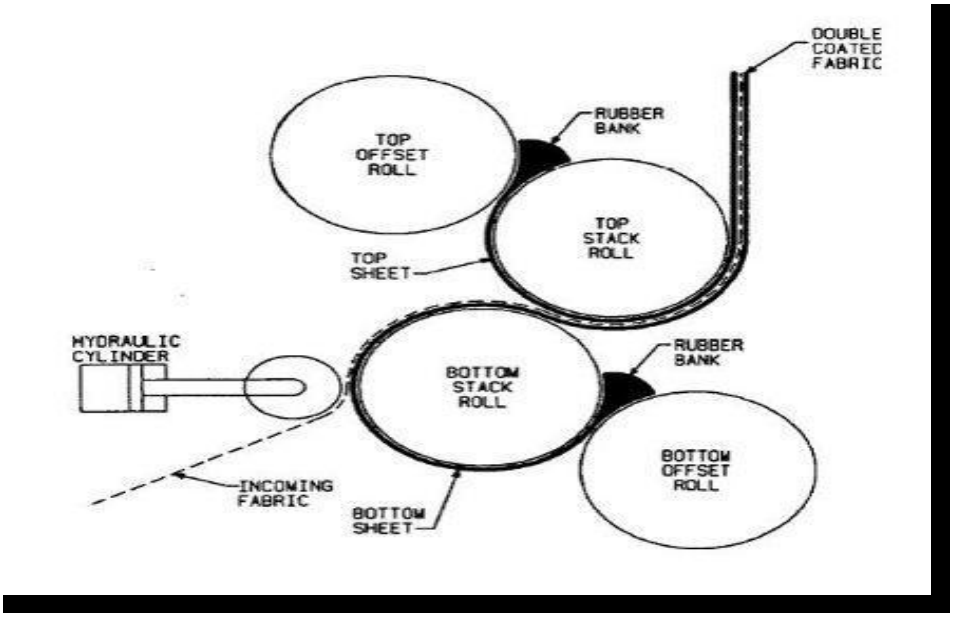


Fig. 3: Rolling method.

5. Semisolid casting method

In semisolid casting method firstly a solution of water-soluble film forming polymer is prepared. 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 appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.[10]

Evaluation Parameters

- ❖ Mechanical properties
- ▪ Thickness

- Dryness/tack test
- Tensile strength
- Young's modulus
- Tear resistance
- Folding endurance

- Organoleptic test
- Surface pH test
- Swelling property
- Transparency
- Assay/content uniformity
- Disintegration test
- In-vitro dissolution test

Thickness

The thickness of film is determined by screw gauge or micrometer at different points of the films. This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.[8]

Dryness/Tack test

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, most of the studies can be adapted intricately to evaluate pharmaceutical orally fast dissolving film. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are available for this study.[24]

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below

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

Percentage elongation

It is calculated by formula

$$\% \text{ Elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Intial length of strip Young's Modulus}}$$

Young's modulus or 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. Hard and brittle strips demonstrate a high tensile strength and young's modulus with small elongation.

Tear resistance

Principally very low rate of loading 51 mm (2 in.) /min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) necessary to tear the specimen is noted as the tear resistance value in newtons (or pounds-force).

Folding endurance

The flexibility of film is an important physical character needed for easy application on the site of administration. The flexibility of the film can be measured quantitatively in terms of folding endurance and is determined by repeatedly folding the film at 180° angle of the plane at the same plane until it breaks or folded to 300 times without breaking. The number of times the film is folded without breaking is computed as the folding endurance value.[25]

Surface pH of film

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. The change in the colour of pH paper was observed and reported.[26,27]

Organoleptic evaluation

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. In-vitro methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations.

Swelling property

Film swelling studies is conducted using simulated saliva solution. Each film sample is weighed and placed in a preweighed stainless steel wire mesh. The mesh containing film sample is submerged into 15ml medium in a plastic container. Increase in the weight of the film was determined at preset time interval until a constant weight was observed.[26,27]

The degree of swelling was calculated using parameters

α = wt - wo/wo

wt is weight of film at time

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

Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film in the rectangular shape and placed inside the spectrophotometer cell. Determine the transparency of the film at 600nm.The transparency of the film can be calculated as follows.[28]

Transparency= (log T600)/b = —єC

Where,

T600= transmittance at 600nm

b= film thickness (mm)

C= concentration

Assay/ Content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.

Disintegration time

Disintegration of orally fast dissolving films requires 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. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films strips.[24]

In-vitro Dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.[24]

Some of the examples of marketed Fast Dissolving Oral Films

Product	Manufactured by	Indication
Caffeine films	Dow chemical company	CNS stimulant.
Dextromethorphan fast dissolving films	Hughes medical corporation	Anti-tussive agent.
Ondansetron Rapidfilms®	Labtec Pharma	Postoperative nausea and vomiting
Chloraseptic® Relief stripsTM	Innozen Inc	Minorirritation, pain and sore throat.
Folic acid fast Dissolving films	Huges Medical Corporation	Anaemia.

CONCLUSION

The growing success and popularity of mouth dissolving film recently in global market is only a need to masking a taste effectively. It is pharmaceutical formulation which is take **"without a water"** the mouth dissolving film have an lots of advantages over the conventional and oral disintegrating tablets. Due to its important during emergency cases like infection hypertension etc. and high patient compliance only because of that so many pharmaceutical companies launching this technology and film can be manufactures due to its uncomplicated equipment and procedure. Due to this mouth dissolving film have economically feasible developmental futuristic opportunities.

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