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A DETAILED REVIEW ON FAST DISSOLVING ORAL FILMS

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ABSTRACT

Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The film is an ideal intraoral fast-dissolving drug delivery system. A large number of drugs can be formulated as mouth dissolving films, for example neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction etc. There are many techniques were available to prepare the oral films at the buccal cavity. Buccal cavity is one the part of mouth and it's having a mucosal layer rapidly absorbs and distributes the body. This review describes about preparation methods of oral films, selection of polymer for formulation, technologies, evaluation parameters and at last applications.

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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. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens [1,2].

Although solid dosage forms are widely accepted by elders and adolescents, younger children tend to prefer liquid formulations that are easier to swallow [3]. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating [4,6], and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available [5,6].

So, Fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms.

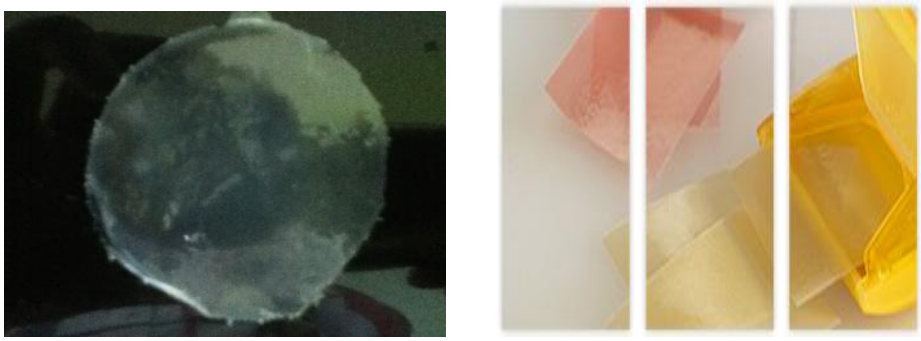


Figure: Examples of Film.

Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention [6,7]. (ODFT) was already popular amongst the people in the early 2000 year with the introduction and widespread use of Listerine pocket strips, a new launch in the mouthwash range.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion in near future [7,8,18]. However only a few products consisting bitter molecules have been able to be commercialized because of the complexity associated with the ODT.

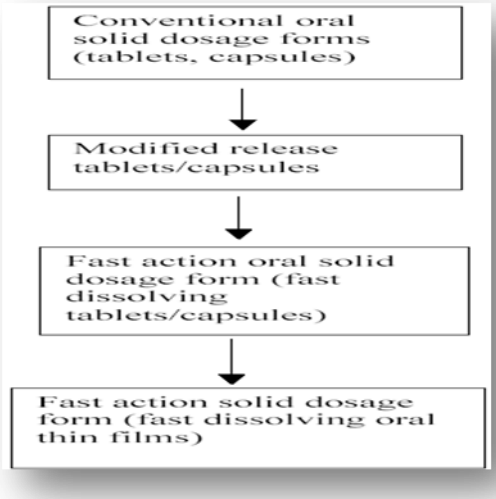


Figure: Flow Chart for the Development of Oral Solid Dosage Form.

Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The development of a fast-dissolving film also provides an opportunity for a line extension in the market place, a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form [7,10-16].

A large number of drugs can be formulated as mouth dissolving films. Innovative products may increase the therapeutic possibilities in the following indications [12,17].

- Pediatrics (Antitussives, Expectorants, Antiasthamatics)
- Geriatrics (Antiepileptic, Expectorants)
- Gastrointestinal diseases
- Nausea (due to Cytostatic therapy)
- Pain (Migraine)
- CNS (Antiparkinsonism therapy)

Salient Features of Fast Dissolving Oral Film

- Ease of administration for patients who are mentally ill-disabled & uncooperative.
- Requires no water; have quick disintegration and dissolution of the dosage form.
- Leaves minimal or no residue in the mouth after administration.
- No risk of choking.
- Provide advantages of liquid medication in the form of solid preparation.
- Amenable and adaptable to existing processing and packaging machinery [9].

Advantages of Fast Dissolving Oral Film

Fast dissolving oral film combines all the advantages of tablets (accurate dose, self-administration) with those of liquid dosage forms (easy swallowing, quick bioavailability).The administration of drugs by the oral route has several advantages[9-10,20-24] over other route of administration such as;

Clinical Advantages:

- Improved oral absorption
- Improved bioavailability due to less amount of degradation of drug.

Medical Advantages:

- Overcomes unacceptable taste of drugs by masking bitter taste of drugs with taste masking agents.
- Improved patient compliance, especially patients suffering from dysphasia and pediatric and geriatric population.

Technical Advantages:

- Contain sugars and other GRAS excipients.
- Improved stability due to better packaging.
- No special set up required for the industry.

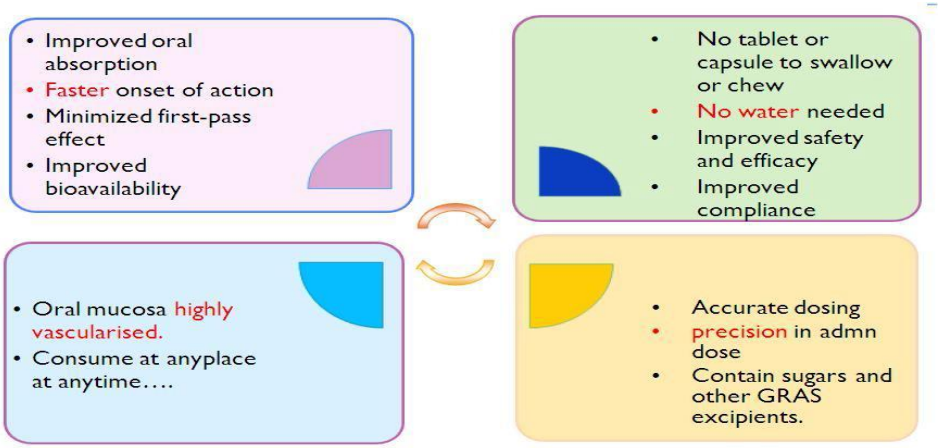


Figure: Advantages of FDOF.

Disadvantages of Fast Dissolving Oral Films

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Taste masking- Most drugs have bitter taste, and need taste masking.
- Special packaging- OFDFs are fragile and must be protected from water so it needs special packaging.
- Dose uniformity is a technical challenge
- Expensive packaging of oral film [7,10,20].

Special features of Fast Dissolving Oral Films

• Thin elegant film
• Available in various size and shapes
• Unobstructive
• Excellent mucoadhesion [7,12,24,30]
• Fast disintegration
• Rapid release

Comparison between Oral Films and Oral Disintegrating Tablets

Table: Comparison between Oral Films and Oral Disintegrating Tablets.

Larger surface area gives greater dissolution	Less surface area gives less dissolution than ODF
ODF are flexible and durable	ODT are brittle and less durable than ODF
Only Low dose can incorporated in formulation	High dose can incorporated in formulation
ODF thickness are 50 to 500 µm	ODT thickness as like convention tablet
Patient Comlpiance is more	Patient compliance is less than FDOF[31-33]

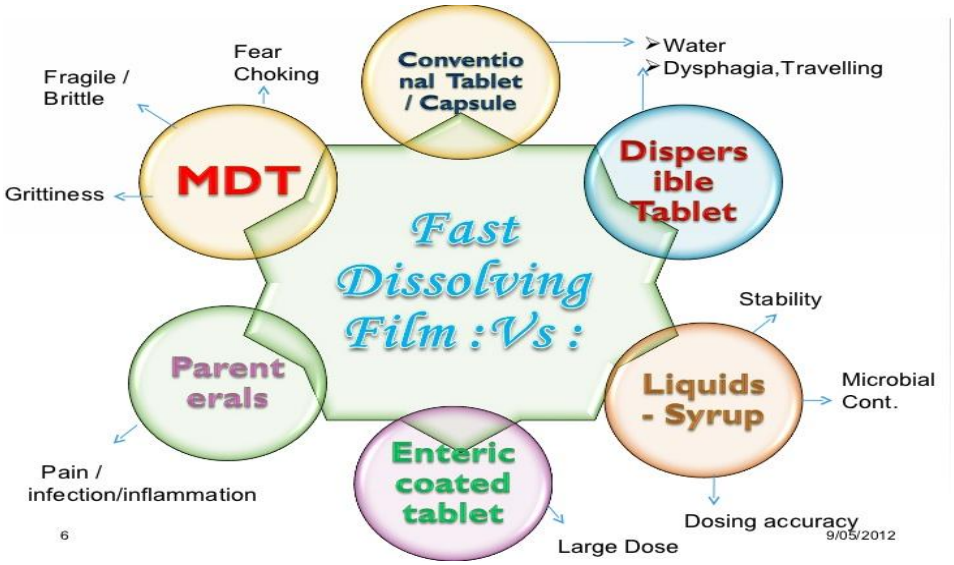


Figure: Comparison of fast dissolving oral film over other dosage forms.

Benefits of Fast Dissolving Oral film over Fast Disintegrating Tablets

- Provide a larger effective surface area for the disintegration.
- No friability loss
- Require less expensive processing and packaging materials
- No fear of choking
- Requires less excipients[20,32]
- Less time consuming process.
- More elegant
- More economical

Classification of Oral Film

The three types of oral films are differentiated from each other in following table.

Table: Classification of Oral Films [33]

Property/sub type	Flash release wafer	Mucoadhesive melt- away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4
Thickness (mm)	20-70	50-500	50-250
Structure	Single layer	Single or multilayer system	Multi layer system
Excipients	Soluble, highly hydrophilic polymers	Soluble, hydrophilic polymers	Low/non-soluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue(upper palate)	Gingival or buccal Region	Gingival, (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes, forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Formulation development

Table: Criteria for selection of Excipients along with their Concentration.

S.NO	CATEGORY	CONC (%)
1.	Drug	1-25
2.	Polymer	40-50
3.	Plasticizer	25-35
4.	Sweetener	2-10
5.	Flavor	2-5

Choice of drug candidate

Suitable drug candidate for FDOF should posses:

- No bitter taste
- Good stability in water and saliva
- Dose should be low as possible.

Figure: Drug Candidates.

SELECTION OF POLYMERS

For the preparation of FDOF the various Polymers can be used in the film up to 40% w/w of the film content. The polymers are responsible for the strength of the film. The film should be tough to prevent damage during handling and transportation. The polymers can be use as single or in combination as per requirement. The examples of the polymers is as follows: Hydroxyl propyl methyl cellulose (HPMC), Hydroxy Propyl cellulose, Starch and modified starch, Pullulan, Pectin Gelatin, Carboxyl methyl cellulose, PVP + Cross linked PVP, Alginates Poly vinyl Alcohol, Malt dextrose etc…

Plasticizer

The role of Plasticizer is beneficial for preparation of Fast dissolving Film. Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the film. The plasticizer should be compatible with polymer and solvent the flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Propylene glycol (PG), Poly ethylene Glycol (PEG), Glycerol, Phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer. Plasticizer may lead to film cracking, splitting and peeling of the film. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug. The Plasticizer should be volatile in nature.

Flavourants

It includes:

1. Both natural and artificial flavour such as artificial vanilla, cinnamon, and various fruit flavours, either individual or mixed.
2. Mints such as peppermint, menthol.
3. Essential oils such as thymol, eucalyptol and methyl salicylate.

Sweeteners

Sweeteners include both natural and artificial sweeteners as:

Natural sweeteners include monosaccharide's, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof;

Water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like and free acid form of saccharin and dipeptide based sweeteners. Aspartame, Neotame are successfully use for the taste masking.

Saliva stimulating agent

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 FDF. Generally acids are used as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%.

METHOD OF PREPARATION

Different methods for achieving fast dissolving film formulation by the following

1. Casting and drying

A. Solvent casting

B. Semisolid casting.

2. Freeze dried wafer

3. Extrusion

A. Hot melt extrusion.

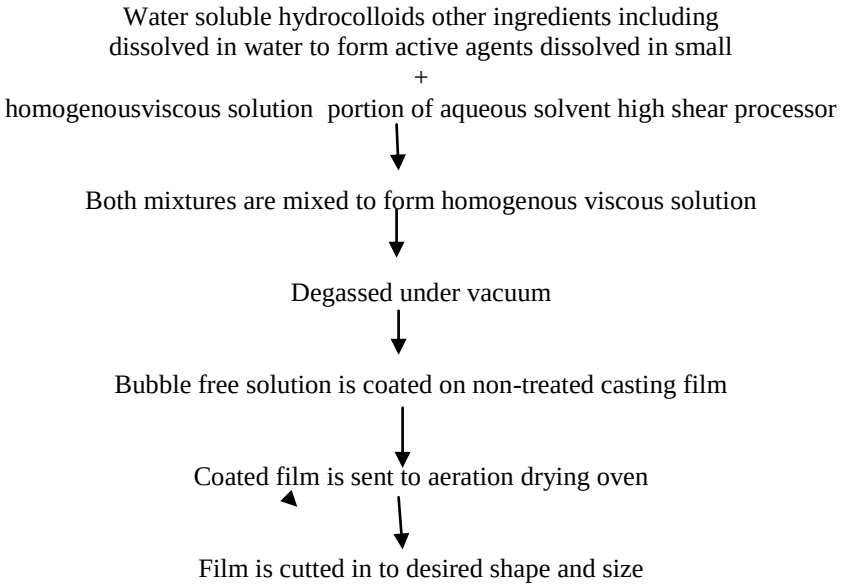
B. Solid Dispersion Extrusion

C. Rolling method.

Casting and drying

Solvent casting Method

- Preparation of the casting solution,
- Deareation of the solution,
- Transfer of the appropriate volume of solution into a mold,
- Drying the casting solution,
- Cutting the final dosage form to contain the desired amount of drug,
- Packaging The Oral fast dissolving films are prepared by dissolving strip forming agents and plasticizer in the distilled water, then solution is continuously stirred up to 4 hours on magnetic stirrer[9,10,12,26] and kept for 1 hour to remove all the air bubbles entrapped. Meanwhile, in the separate container remaining water soluble excipients i.e. sweetening agent, saliva-stimulating agent, flavor and drug are dissolved with constant stirring for 45 min. When the stirring is over both the solutions are mixed together with stirring for another 1 hour on magnetic stirrer. Then keep the solution stationary for 1 hour to let the foams settle down. The resulting formulation is casted on a suitable platform and is dried to form a film. The film is preferably air-dried or dried under oven then the film is carefully removed.



Advantages

- Great uniformity of thickness and greatclarity then extrusion.
- A typical relative standard deviation (RSD) for uniformity testing of an oral thin-film batch prepared by liquid casting is on the order of 1.2% RSD.
- Films have fine gloss and freedom from defects such as die lines.
- Films have more flexibility and better physical properties. The preferred finished film thickness is typically 12-l00µm.

Disadvantages

>The polymer must be soluble in a volatile solvent or water.
>A stable solution with a reasonable minimum solid content and viscosity should beformed.
>Formation of a homogeneous film and release from the casting support must bepossible.

Semisolid casting:

In the semisolid preparation water soluble polymer add in it and this preparation add in acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate) which is prepared by the ammonium, sodium hydroxide then finally addsufficient amount of plasticizer form a gel and it casted[9,12,26]. Acid insoluble polymer with film forming polymer ratio is 1:4 and film thickness is 0.015 to 0.05 inches.

Freeze dried wafer

Is also known as Lyophilisation or Cryodessication method in that dehydration of water and reduce pressure from surrounding to allow the water in material to sublime directly from solid phase to gaseous phase. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

Extrusion

Hot melt extrusion

In the hot melt extrusion drug mixed with carrier in the solid form. Extruder having extra facility with heater it melt the solid form carrier and drug then this melt is place in the dies and cut in to specific shape[9-10,12,26].

E.g. Maltodextrin can be used to produce fast-dissolving films with a high drug loading capacity by hot-melt extrusion technology.

Advantages

>Noneed to use solvent or water.
>Fewer processing steps.
> Compressibility properties of the APT may not be of importance.
> Good dispersion mechanism for poorly soluble drugs.
> More uniform dispersion of the fine particles because of intense mixing and agitation.
>Less energy compared with high shear methods.

Disadvantages

>Thermal process so drug/ polymer stability problem.
>Flow properties of the polymer are essential to processing.
>Limited number of available polymers

Solid Dispersion Extrusion:

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. In this method[9,10,12,26] drug is dissolved in a suitable liquid solvent then solution is incorporated into the melt of polyethylene glycol, obtainable below 70˚C and finally the solid dispersions are shaped into the films by means of dies.

Rolling method:

In this preparation drug containing suspension having water or alcohol as solvent is added on drum then evaporated the solvent[9,10,12,26] and cut in specified shape.

VARIOUS TECHNOLOGIES USED IN ORAL FILM FORMULATION

XGel:

XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.

Soluleaves:

This is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. Solute leaves technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form.

Wafertab:

Wafertab is a patented delivery system that uses a unique process to prepare drug-loaded thin films which can be used in topical
or oral application. Active ingredients are incorporated into the film after casting.

Foamburst:

Foam burst is a new patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure.

The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt-in-the mouth sensation [9,33].

Micap:

Micap Signed an option agreement in 2004 to combine its expertise inmicro encapsulation technology with the Bio Progress water-soluble films.

Patented Technologies:

The patented technologies for manufacturing of fast dissolving drug delivery system are Zydus, Orasolv, Durasolv, Flashdose, Wowtab and Nanocrystal Technology.

EVALUATIONS

Weight Uniformity:

Films can be weighed on analytical balance and average weight can be determined for each film. It is useful to ensure that a film contains proper amount of excipients and drug.

Thickness:

The thickness of film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

DrynessTest/Tack Tests:

About eight stages of film drying process have been identified and they are set-to touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat dry print free. 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 also available for this study[7,10,12,22,26].

Tensile Strength:

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

$$\text{Tensile strength} = \frac{\textbf{Load at failure} \times \textbf{100}}{\textbf{Film thickness} \times \textbf{Film width}}$$

pH value:

The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH.

Tear resistance:

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically, 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) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds-force).

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 as follows:

$$\text{Young's modulus} = \frac{\textbf{Slope} \times \textbf{100}}{\textbf{Stripthickness} \times \textbf{Crossheadspace}}$$

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

Folding endurance:

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

Disintegration time:

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s.

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.

Assay/drug content and 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.

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. [34]

List of Marketed Fast Dissolving Oral Films

Table: List of Marketed FDOF.

S.No.	Product	Manufactured By
1	Dextromethorphan HBr (cough suppressant),Diphenhydramine Citrate (cough and cold),Breath Strips	MonoSolRx
2	Donepezil rapid dissolving films, Ondansatron rapid dissolving films	Labtec Pharma
3	Life-saving rotavirus vaccine to infants	Johns-Hopkins undergraduate biomedical engineering students.
4	Methylcobalamin fast dissolving films, Diphemhydramine HCl fast dissolving films, Dextromethorphan fast dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films	Hughes-medical corporation
5	Altoid cinnamon strips, Boots vitamin c strips, Cool shock peppermint strips, Benzocaine films, Caffeine films	Dow-chemical company

APPLICATIONS OF FAST DISSOLVING ORAL FILMS

Oral films are preferred for local action and also to manage pain, allergies, sleeping difficulty and CNS disorders [26-28].

Topical applications:

The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other applications.

Gastro retentive dosage systems:

Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract, and used to treat gastrointestinal disorders.

Diagnostic devices:

Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

Vaccines:

Fast dissolving films can be delivered in the form of vaccine which is stable at room temperature so it is quickly dissolved in mouth and in saliva. Rotavirus vaccine prepared in United States is room temperature stable fast-dissolving buccal film delivery system for vaccines.

- Oral films are applicable to enhance the bioavailability of poorly bioavailable drugs.
- Taste masking of bitter drugs.
- Dissolvable films are loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device.

CONCLUSION

Recently Fast dissolving films have gained popularity as dosage forms for the mouth fresheners. Meanwhile pharmaceutical industries have recognized their potential for delivering medicinal products and have launched several products for the OTC market using this technology. The fast dissolving thin film are hardly described and investigated in literature, but seem to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Due to lack of standard methodology for preparation and analysis products existence in the market is limited.

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