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A Complete Review on Mouth Dissolving Films

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ABSTRACT
Mouth Dissolving Films (MDFs) are one such novel approach to increase consumer acceptance by rapid dissolution, and self-administration without water or chewing. This dosage form allows the medication to bypass the first-pass metabolism so the bioavailability of the medication is improved. It has the potential to improve the onset of action, lower the dosing and eliminate the fear of choking in geriatrics and paediatrics. Also used for the taste masking of widely bitter-tasting drugs that are most important for paediatric patients. A large number of drugs can be formulated as mouth dissolving films, for example, neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic drugs for erectile dysfunction, etc. This review article gives an idea about formulation techniques, mechanism, evaluation parameters, an overview of packaging, applications, and some available marketed products of mouth dissolving films.

I. INTRODUCTION

The administration of therapeutic agents most commonly follows the oral route for drug administration. Oral dosage forms are more popular than other dosage forms because of ease of administration, accurate dosage, self-medication, pain avoidance, patient compliance, etc. Sterile conditions are not required for a solid oral delivery system; therefore, their manufacture is less expensive.[2]The oral route is the most preferred route by medical practitioners and manufacturers due to the highest acceptability by the patients.[7]

The popular oral solid dosage forms are capsules and tablets. Children, geriatric patients, and many other people including disabled patients often have trouble swallowing tablets or capsules furthermore, dosing is an issue, as most medications are available in doses that are significantly too large for the paediatric population and cannot easily and reproducibly be divided into smaller doses.[2]Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs while improving patient compliance.[1]Bio-adhesive mucosal dosage forms including adhesive tablets, gels, and patches are outcomes of technological development. Among various dosage forms, the use of polymeric films for delivering medication into the buccal cavity has developed great potential in the recent era (Arya et al., 2010).[4]

Oral disintegrating tablets (ODTs) and Mouth Dissolving films (MDFs) are typical examples of orally disintegrating drug delivery systems. These systems were developed in the late 1970 to serve as an alternative to conventional dosage forms.A typical MDF is usually equal to the size of a postage stamp.[7] Mouth Dissolving Films (MDFs), when placed on the tongue, immediately hydrate by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agents from the dosage form. MDFs are a kind of formulations that are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. The sublingual mucosa has a thin membrane and large veins are more permeable (Barnhart and Sloboda, 2007b). It gives instantaneous bioavailability of drugs due to rapid blood flow.[6] MDFs design permits the incorporation of a variety of drugs for their pharmacological effects e.g., antitussive, anti-epileptic, anti-asthmatic, expectorant, neuroleptics, cardiovascular, analgesics, drugs for erectile dysfunction, etc.[6]

Anatomy and Physiology of oral mucosa
The **oral mucosa** isthe mucous membrane lining the inside of the mouth. It comprisesstratified squamous epithelium, termed "oral epithelium", and an underlying connective tissue termed lamina propria.
Oral mucosa is divided into three main categories based on function and histology:

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1. Lining mucosa, nonkeratinized stratified squamous epithelium, found almost everywhere else in the oral cavity, including the:
(a) Alveolar mucosa, the lining between the buccal and labial mucosae. It is bright red, shiny, and smooth with many blood vessels, and is not connected to underlying tissue by rete pegs.
(b) Buccal mucosa, the inside lining of the cheeks and floor of the mouth; part of the lining mucosa.
(c) Labial mucosa, the inside lining of the lips; part of the lining mucosa.
2. Masticatory mucosa, keratinized stratified squamous epithelium, found on the dorsum of the tongue, hard palate, and attached gingiva.
3. Specialized mucosa, specifically found in the regions of the taste buds on lingual papillae on the dorsal surface of the tongue; contains nerve endings for general sensory reception and taste perception.[8]

Taste is one of the important parameters in the formulation of mouth dissolving films. Taste masking is done for bitter drugs and since the mouth dissolving films are supposed to be placed on the tongue, taste masking becomes essential for patient compliance as well. There are five tastes located on different receptors on the tongue, sensations for sweet are located at the tip of the tongue, and sensations for sour are located at the sides of the tongue whereas bitterness at the back of the tongue and salty sensations are located at the sides and tip of the tongue and umami produced by monosodium glutamate mainly found in meat and fish. These above taste receptors bind molecules down by saliva and transmit electrical impulses by the 7th, 9th and 10th cranial nerves to these areas of the brain that participate in the perception of taste.[8]

The enzymes and the mouth's moist environment within its secretions help to soften food, facilitating, swallowing, and beginning the process of digestion. The salivary glands secrete mucin as part of saliva. Saliva pH ranges from 6.8 to 7. The permeability of buccal mucosa is found to be 4000 times greater than skin.[2]

Mechanism of drug absorption from oral mucosa

The delivery system is simply placed on any oromucosal tissue or patient's tongue. The film once placed in the oral cavity is instantly wet by the saliva. The film rapidly dissolves and hydrates to release the medication for oromucosal absorption. The presence of hydrophilic polymer and other excipients helps in better disintegration and dissolution of the drug from the films. A drug that penetrates through the oral mucosa passes through a network of capillaries and arteries and reaches the systemic circulation.[2]

1.FEATURES OF MDF

- It should be thin, flexible, and easy to handle.
- The films should be transportable, not sticky, and keep a plane form without rolling up.
- Available in various sizes and shapes.
- Give a pleasant mouth feel.
- Have an acceptable taste.
- Unobstructive.
- Fast disintegration.
- The dosage form can be consumed at any place and anytime as per the convenience of the individual.
- It should be cost-effective and convenient for commercial production.[2],[5],[10]

2.ADVANTAGES

- Rapidly dissolve and disintegrate in the oral cavity because of the large surface area that lowers the dosage interval.
- The quick onset of action, efficacy, and safety profile.
- Improved patient compliance, especially patients suffering from dysphoria and paediatric population.
- Improved stability due to better packaging.
- Oral films are desirable for patients suffering from motion sickness, dysphoriarepeated emesis, and mental disorders.
- It should be more flexible, compliant, and not as brittle as ODTs (Orally disintegrating Tablets).
- From a commercial point of view, oral films provide a new business opportunity like product differentiation promotion, etc.[2],[6]

3.DISADVANTAGES

- We cannot incorporate high doses into strips or films.
- Maintaining dosage uniformity is a challenging task for the films.
- Moisture sensitivity
- Requires special packaging for product safety and stability.
- Hygroscopic in nature so it must be kept in dry places.
- Drugs that are unstable at buccal pH cannot be administered by this route.
- Drugs that irritate the mucosa cannot be administered.[2],[5],[10]

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4.CLASSIFICATION OF ORAL FILMS

There are three different subtypes:

a) Flash release.

b) Mucoadhesive melt-away wafer.

c) Mucoadhesive sustained-release wafers.[2]

Table 1: Difference types of films.[2]

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

Drug delivery through the oral cavity can be subdivided as follows

Sublingual delivery:

This is the systemic delivery of drugs through the mucosal membranes lining the floor of the mouth (sublingual mucosa). The sublingual region shows higher drug permeability than the buccal region. Drugs that require rapid onset of action are administered by this route e.g., Nitro-glycerine.

Buccal delivery:

The drugs administration through mucosal membranes lining the checks and the area between gums, upper and lower lips to the systematic circulation.

Local delivery:

Which is drug delivery in the oral cavity for the treatment of conditions of the oral cavity principally aphthous ulcers, fungal conditions, and periodontal.

5.FORMULATION ASPECTS AND COMPOSITION OF MDF

Formulation of oral dissolving film (ODF) involves the intricate application of aesthetics and shows characteristics such as taste masking, fast-dissolving, physical appearance, mouth feel, etc. The excipients used in formulations of oral dissolving film are given below as per their categories.[2]

- (i) Active pharmaceutical ingredients
- (ii) Strip-forming polymers
- (iii) Plasticizers
- (iv) Sweetening agents
- (v) Saliva stimulating agents
- (vi) Flavouring agents
- (vii) Colouring agents
- (viii) Stabilizing and thickening agents
- (ix) Surfactants

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Table 2: General composition of MDF.[10]	
Ingredients	**Concentration percentage**
API (drug) API: Active pharmaceutical ingredient	01–25
Plasticizer	00–20
Flavouring agents	02–10
Sweetening agents	03–06
Hydrophilic polymer/film former	40–50
Saliva stimulating agent	02–06
Colour	01
Surface active agent	Quantity sufficient

(i) Active pharmaceutical ingredients:

Several classes of drugs can be formulated as mouth dissolving films including antiulcer (e.g., omeprazole), antiasthmatic (salbutamol sulphate), antitussives, expectorants, antihistaminic(cetirizine), NSAID'S (e.g., paracetamol, diclofenac meloxicam, valdecoxib). Chlorpheniramine maleate (Antiallergic), Zolmitriptan. Generally, 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in the OS18.[8]

Ideal Characteristics of a Suitable Drug Candidate:

- The drug should have a pleasant taste. (Not bitter).
- The low dose should have up to 40 mg.
- Drugs with minor and moderate molecular weight are preferable.
- The drug should have good solubility and stability in saliva as well as in water.
- Drugs should have the ability to permeate oral mucosal tissue through prepared oral film. Examples: antiallergic, antiemetic, antimigrant, etc.[2]

Table 3: Suitable drug molecules that can be loaded into the oral film/ strip (Sohi et al., 2004).[6]		
Molecule	**Dose (mg)**	**Therapeutic category**
Acrivastine	8	Antihistaminic
Azatidine maleate	1	Antihistaminic
Cetirizine	5-10	Antihistaminic
Chlorpheniramine maleate	4	Anti-allergic
Diphenhydramine HCl	25	Antihistaminic
Dicyclomine	25	Muscle relaxant
Dextromethorphan HCl	10-20	Cough suppressant
Desloratadine	5	Antihistaminic
Famotidine	10	Antacid
Flurazepam	15-30	Anxiolytic, Anticonvulsant
Ketoprofen	12.5-25	Anti-inflammatory
Loperamide	2	Anti-diarrheal
Loratadine	5-10	Antihistaminic
Nitro-glycerine derivatives	0.3-0.6	Vasodilators
Nicotine	1-15	Smoking cessation
Oxycodone	2.5-10	Opioid analgesic
Omeprazole	10-20	Proton pump inhibitor
Sumatriptan succinate	35-70	Antimigraine
Trip Alodine HCl	2.5	Antihistaminic
Zolmitriptan	2.5	Anti-migraine

(ii) Film-forming polymers:

Fast dissolving film is prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. "Water-soluble polymers" are

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used as film formers for fast dissolving films. The water-soluble polymers give rapid disintegration; good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water-soluble polymers used as film former are HPMC E3, E5 and E15, and K-3; Methylcellulose A-3, A-6, and A-15; Pullulan; carboxymethylcellulosecekol 30; Polyvinylpyrrolidone PVP K-90; Pectin; Gelatine; Sodium Alginate; Hdroxypropylcellulose; Polyvinyl alcohol; Maltodextrins and Eudragit RD 108, 9, 10, 11, 12; Eudragit RL100. Polymerized rosin is a novel film-forming polymer.[7]

Ideal properties of the film-forming polymers:

- The polymer employed should be non-toxic, non-irritant, and devoid of leachable impurities.
- It should have good wetting and spreadability property.
- The polymer should exhibit sufficient peel, shear, and tensile strengths.
- The polymer should be readily available and should not be very expensive.
- It should have a good shelf life.
- It should not aid in causing secondary infections in the oral mucosa/ dental region.
- It should have a good mouth feel property.[7]

Table 4: Properties of different polymers used in the formulation of oral films (Kulkarni et al., 2010).[6]

Polymer Used	Disintegration Time (sec)	Appearance	Film Forming Capacity
HPMC E-15+ PEG 400	120	Transparent	Good
HPMC E-15+ Glycerine	92	Transparent	Good
HPMC K4M	-	-	Very poor
HPMC E-15+ Pullulan	-	-	Poor
HPMC E-15+ PVA	78	Transparent	Average
HPMC E-15+PVP	67	Transparent	Average
HPMC E- 15+PVA+MCC	-	-	Poor
HPMC E-15+MCC	42	Semi transparent	Better
PVA	52	Transparent	Average
PVA+PVP+ Glycerine	64	Transparent	Average
PVA+PVP+ PEG 400	52	Transparent	Average
PVP	-	-	Very poor
Pullulan+PVA	-	-	Very poor
Pullulan+ Guar Gum+ Xan-than Gum+ Carrageenan	19	Transparent	Best
Gelatine	-	-	Very poor
Eudragit RL-100	-	-	Very poor

(iii) Plasticizers:

Plasticizers improve the strength and flexibility of the polymeric matrix. Plasticizers are chosen based on the polymers involved and the method used for formulation. They decrease the brittleness of the polymer film and also improves the flexibility of the film. The selection of plasticizers depends upon the compatibility of the polymer, the nature of the solvent, and the method of formulation. By lowering the glass transition temperature of the polymers more structurally pleasant, stronger, and more flexible film can be prepared. Most commonly used plasticizers are glycerol, propylene glycol, PEG, phthalate derivatives such as dimethyl, diethyl, and dibutyl phthalate, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin, and castor oil. 0-20% w/w plaster concentration is used for preventing cracking, splitting, and peeling of the strip (Rowe and Forse, 1980).[6]

(iv) Sweetening agents:

Sweeteners include both natural and artificial sweeteners: Natural sweeteners include monosaccharides, disaccharides, and

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polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolysed 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, acesulfame-K and the like and free acid form of saccharin and dipeptide based sweeteners. Aspartame and Neotame are successfully used for taste masking.[1]

Table 5: List of FDA-approved Non-NutritiveSweeteners (Sweetness factor, Sucrose = 1).[8]

Sr.No.	Sweetener	Sweetness Factor
1	Aspartame	180-200
2	Sucralose	600
3	Acesulfame K	200
4	Neotame	7000-13000
5	Saccharin	300

(v) Saliva stimulating agents:

The oral mouth dissolving films disintegrate on coming in contact with the liquid in the oral cavity which is essentially saliva. Saliva Stimulating Agents produce saliva that helps in the quick disintegration and dissolution of the films. The increased saliva productions facilitate the faster disintegration and rapid dissolution rate. Saliva stimulating agents are used in concentrations of 2-6% w/w of the film either used alone or in combination. Examples: Citric acid, Lactic Acid, and Ascorbic acid.[2]

(vi) Flavouring agents:

These are the most important agents which are to be added to the pharmaceutical oral preparations because flavours are the ultimate goal for the choice of the preparations by the patients. It might have become an important factor in the sale of products. Both natural and artificial flavours are used. The amount of flavour required to mask the taste depends on the flavour type and its strength. Preferably up to 10%w/w flavours are added to the formations. Flavouring agents can be selected from synthetic flavour oils, oleo resins, and extract derived from various parts of the plants like leaves, fruits and flowers. Flavours can be used alone or in combination. Peppermint oil, cinnamon oil, spearmint oil, and oil of nutmeg are examples of flavour oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavours. Apple, raspberry, cherry, and pineapple are a few examples of fruit essence types.[7]

Table 6: Flavouring agents for taste masking.[8]

Basic Taste	Masking agents
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint
Bitter	Wild cherry, walnut, chocolate, mint, anise
Sweet	Vanilla, fruit and berry
Sour	Citrus flavour, liquorice, root, beer, raspberry

(vii) Colouring agents:

Colouring agents are used to increase the appeal of the film. Pigments are used as colouring agents. In mouth dissolving films, titanium dioxide is the most widely used colorant and in various other pharmaceutical preparations too. A full range of colours are available including FD and C, custom Pantone- matched and natural colours. In fast dissolving film, the colouring agent is not exceeding concentration level of 1% w/w.[2]

(viii) Stabilizing and thickening agents:

To improve the viscosity and consistency of the formulation, the stabilizing and thickening agents are incorporated. Natural gum, like xanthan gum, carrageenan, locust bean gum and cellulose derivative is loaded up to 5% w/w.[6]

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(ix) Surfactants:

Surfactants are used as a solubilising or wetting or dispersing agent so that the film is getting dissolved within seconds and releases the active agent immediately. Some of the commonly used are:

- Sodium lauryl sulphate, benzalkonium chloride, benzethonium chloride, tweens etc.
- The most important surfactant is polaxamer407 which is used as solubilizing, wetting and dispersing agent.[8]

6.METHOD OF PREPARATION

Different methods for achieving fast dissolving film formulation by the following:

- Casting and drying

A. Solvent casting

B. Semisolid casting

- Freeze dried wafer
- Extrusion

A. Hot melt extrusion

B. Solid Dispersion Extrusion

C. Rolling method

- Using Ion Exchange Resin

1. CASTING AND DRYING

A. Solvent casting

- Preparation of the casting solution,
- De-aeration of the solution,
- Transfer of the appropriate volume of solution into a mould,
- Drying the casting solution,
- Cutting the final dosage form to contain the desired amount of drug,
- Packaging.[1]

The oral fast dissolving films are prepared by dissolving strip forming agents, plasticizer and saliva stimulating agent in the distilled water, then the solution is continuously stirred on a magnetic stirrer followed by removing all the air bubbles entrapped in it and kept for 1 hour. In another container water-soluble excipients i.e., disintegrating agent, saliva stimulating agent, sweetening agent, flavouring agent and drug are dissolved with constant stirring. When the stirring is over both the solutions are mixed with stirring for another 1 hour on a magnetic stirrer. Then the solution is kept for 1 hour to let the foam settle down. The resulting formulation is dried to form a film. The film is preferably dried or air-dried or oven-dried, and then the film is carefully removed.[2]

B. Semisolid casting

In the semisolid casting method, 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 the appropriate amount of plasticizer is added so that a gel mass is obtained. Finally, the gel mass is cast into 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.[8]

2. FREEZE-DRIED WAFER

It is also known as Lyophilisation or Cryodesiccation is a method in which dehydration of water takes place. The pressure is reduced from the surroundings so as to allow the water in the material to sublime directly from a solid phase to a gaseous phase.Lyophilization results in to preparations which are highly porous with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.[1]

3. EXTRUSION

A. Hot melt extrusion

Hot melt extrusion is a technique in which a mixture containing drug, polymer and excipients is extruded under high temperature to form a homogenous mass which was then coated to form smooth films.[5] All substances required to make the films were in their solid powder form.[10]

This process has a lot of advantages: -

- Fewer unit operations
- Better content uniformity.[8]
- An anhydrous process.[8]
- A dispersion mechanism for poorly soluble drugs.[8]
- A low-energy alternative to high-shear granulation.[8]
- Less processing time compared with conventional wet granulation.[8]
- Involves lower temperature and shorter residence times of the drug carrier mix, absences of organic solvents, continuous operation possibilities, minimum product wastage, better control of operating parameters and possibilities to scale up.[7]

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B. 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.[2] In this method, drugs are dissolved in suitable solutions and solvents and are incorporated into the dissolved polyethene glycol below 700 C. And then these are designed into thin films using dies.[10]

C. Rolling method

In the rolling method, a solution or suspension containing a drug is rolled on a carrier.[8]The film is formulated by preparation of pre-mix, by adding active, there is the subsequent formation of the film (Rathi et al., 2011). The pre-mix batch includes a film-forming polymer, polar solvent and other ingredients except API added to the master batch feed tank. A predetermined amount of the master batch is fed by the first metering pump and control valve. A desired amount of drug is added to the mixer and then blended for a sufficient time to form a homogenized matrix. A specific amount of matrix is fed into the pan through the second metering pump. The metering roller determines the thickness of the film. The film is finally formed on a substrate and carried away by the support roller. It is dried by using controlled bottom drying.[6]

4. USING ION EXCHANGE RESIN

Ion exchange resins are high molecular weight polymers with cationic and anionic functional groups. Ion exchange resins contain positively or negatively charged sites and are accordingly classified as either cation or anion exchangers. They are further classified as inorganic and organic resins. Due to their high molecular weight, they are not absorbed by the body which makes them safe for human use. The most frequently employed polymeric network is a copolymer of styrene and divinylbenzene. Ion exchange resins are used in formulations for stabilization of sensitive components, sustained release of drugs, providing tablet disintegration and taste masking. Drug resin complex dissociation does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odour of the drug.Pulsion 335 is a weak acid cation exchange polyacrylic resin with carboxylic acid as a functional group. It possesses good taste masking ability and is supplied in powder.[8]

7. VARIOUSTECHNOLOGIES USED IN ORAL FILM FORMULATION

1. XGel: XGel film Technology developed by BioProgress is causing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry.[1]XGel film potentially enhances product stability. It has also been developed for non-ingestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices.[7]
2. Soluleaves: This is applied to flavour-release products such as mouth fresheners, confectionery, and vitamin products. Solute leaves technology can be used to deliver active ingredients to the oral cavity efficiently and in a pleasant and easily portable form.[1]The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as nutritional products. Soluleaves films can also be designed to adhere to mucous membranes and to release the active ingredients slowly over 15 minutes.[7]
3. 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 applications. Active ingredients are incorporated into the film after casting.[1]Wafertab system lends itself to many possibilities for innovative drug design, enabling multiple films with different actives to be bonded together.[7]
4. Foamburst: Foamburst 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.[1]
5. Micap: Micap Signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress water-soluble films.[1]

The developments aimed at providing new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs).[7]

6. Patented Technologies: The patented technologies for the manufacturing of fast

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dissolving drug delivery systems are Zydus, Orasolv, Durasolv, Flashdose, Wowtab and Nanocrystal Technology.[1]

8. EVALUATION PARAMETERS

1. Organoleptic evaluation - For psychophysical evaluation of the product, special controlled human taste panels are used. This in-vivo taste evaluation is carried out on human volunteers. In-vitro taste evaluation of ODFs is performed by using taste sensors for screening. In vitro taste assessing methods and technologies are appropriate and sufficient for high-throughput taste sensing of such dosage forms. Both in vivo and in vitro techniques analyse the taste masking ability and sweetness level of taste masking agents.[4]
2. Weight Uniformity: Films can be weighed on an analytical balance and the average weight can be determined for each film. It is useful to ensure that a film contains a proper number of excipients and drugs.[1]
3. Appearance/ Visual inspection: All prepared films were checked for their appearances whether they are transparent or opaque.[8]Visual inspection of a prepared orodispersible film gives information about color, homogeneity, and transparency.[4]
4. Mechanical properties

1) Thickness: The thickness of film should be measured with the help of a micrometre screw gauge or calibrated digital vernier callipers. The film should be measured at five points i.e., from the centre and all the four corners, and then the mean thickness is calculated. It is necessary to determine the uniformity of thickness as it is directly related to the accuracy of dose in the film.[7]
2) Dryness test/Tack test: About eight stages of the 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.[1]
3) Tensile strength: Tensile strength is defined as the maximum stress applied at which the film breaks. This test is performed to measure the mechanical strength of films. It can be calculated from the applied load at rupture divided by the strip cross-sectional area given in the equation: **Tensile strength = (Load at failure/film thickness x film width) x 100**.[4]
4) Percentage elongation: When the sample films are subjected to tensile stress, deformation of the films occurs resulting in stretching or elongation of a sample. It is performed to predict the ductility of polymers using a texture analyser.

Percent elongation= L*100/Lo.[5]

L = Increase in length of the film, Lo = Initial length of a film

5) Tear resistance: Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. A 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).[1]
6) Young's modulus: Young's modulus or elastic modulus is the measure of the stiffness of a strip. It is represented as the ratio of applied stress over the strain in the region of elastic deformation as follows: **Young's Modulus= (Slope / Strip thickness x Cross head speed) x 100**

Hard and brittle strips demonstrate high tensile strength and Young's modulus with small elongation.[1]

7) Folding endurance: Folding endurance is determined by repeat folding of the strip at the same place till the strip breaks. The number of films folded without breaking is computed as the folding endurance value.[2]
8) Swelling property: Simulated saliva solution is used to check the swelling studies of films. The initial weight of the film is determined and is placed in pre-weighed stainless steel wire mesh. This mesh-containing film is then dipped into a simulated saliva solution. An increase in the weight of the film is noted at constant predetermined time intervals until no more increase in weight.

Degree of swelling = Wt – Wo/ Wo

Wt = weight of the film on time t

Wo = weight of the film on time zero.[4]

5. Transparency: The transparency of a strip is determined by using a UV-spectrophotometer. This test is performed for the visual appearance of the formulation. Film specimens are cut into rectangular shapes and placed on

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the internal side of the photometer cell. The transmittance of the film is worked out at 600 nm wavelength. The formula for determining transparency is given (Mandeep et al., 2013):

Transparency = (logT600)/b = -€c

T600= transmittance at 600 nm, b= film thickness (mm), c = concentration.[4]

6. Contact angle: The goniometer determined the contact angle at room temperature. Put a drop of double distilled water on the dry film surface. Image of water droplet recorded within 10sec of deposition by using a digital camera. To determine the angle, analyse a digital picture. The contact angle was measured on both sides of the drop and averaged.[6]
7. Assay/drug content and content uniformity: This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeias. Content uniformity is determined by estimating the API content in an individual strip. The limit of content uniformity is 85–115 per cent.[1]
8. Disintegration time: The disintegration apparatus mentioned in official pharmacopoeias is used for determining the disintegration time of a film. Normally, the disintegration time is the function of the composition of film as it varies with the formulation and generally ranges from 5 to 30 s. Mostly, the USP disintegration apparatus is used for this test. There are no official guidelines available for determining the disintegration time of orally fast disintegrating films. There are two methods for determining the disintegration time of the film.[5]

1) Slide frame method: A drop of distilled water is poured onto the film clamped into slide frames placed on a petri dish. Time is taken by the film to dissolve noted.[5]
2) Petri dish method: A film is placed into 2 ml distilled water and taken in a Petri dish. Time taken by the film to dissolve completely is considered disintegrating.[5]

9. In-vitro dissolution test: Dissolution testing can be performed by using the standard paddle or basket apparatus described in any of the pharmacopoeias. The dissolution medium mainly is selected as per the sink conditions and the highest dose of the API. Many times the dissolution test can be difficult due to the tendency of the strip to float onto the dissolution medium when the paddle apparatus is in use.[2]
10. Surface Morphology: For surface morphology, scanning electron microscopy is performed at fixed magnification.[4]
11. pH value: The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. The film must have nearly uniform ph.[1]Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation.[5]
12. Moisture loss: Percent moisture loss is a parameter that determines the hygroscopicity of a film. Usually, this parameter is determined by first finding the initial weight of the film, afterwards, putting this film in a desiccator for three days. The desiccator contains calcium carbonate. After three days, strips are taken out and weighed again. Moisture loss is determined by applying the following formula: **Percentage moisture loss = [(Initial weight - Final weight) / Initial weight] x 100**.[4]
13. Moisture uptake: Moisture uptake of a film is determined by first cutting the film with the dimension of 2 x 2 cm2. Afterwards, these strips are exposed to an environment with a relative humidity of 75% at room temperature for 7 days. Moisture uptake is determined as the per cent weight gain of the strips.

Percentage moisture uptake = [(Final weight - Initial weight) / Initial weight] x 100.[4]

14. Stability Studies: Stability studies on the optimized oral fast dissolving film are carried out to determine the effect of temperatures and humidity on the stability of the drug. The film is stored in an aluminium foil and subjected to stability at room temperature. The sample can withdraw at 3 months and 6 months and be subjected to cumulative % drug release and in vitro dissolution studies to determine disintegration time and disintegration test.[2]

9. PACKAGING

In the pharmaceutical industry, the package selected adequately must preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. APR- Labtec has developed the Rapid card, a proprietary and patented packaging

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system, which is specially designed for Rapid films. The rapid card has the same size as a credit card and holds three rapid films on each side. Every dose can be taken out individually.[7],[9] The material selected must have the following characteristics:

• They must protect the preparation from environmental conditions.
• They must be FDA approved.
• They must meet the applicable tamper-resistant requirement
• They must be non-toxic.
• They must not be reactive with the product.
• They must not impart to the product tastes or odours.[7],[9]

1. Foil, paper or plastic pouches: The flexible pouch is a packaging concept capable of providing not only a tamper-resistant package but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminium pouches.[7],[9]
2. Single pouch and Aluminium pouch: Soluble film drug delivery pouch is a peel-able pouch for "quick dissolve" soluble films with high barrier properties. The pouch is transparent for product display. Using a 2-structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single-dose pouch provides both product and dosage protection. The aluminium pouch is the most commonly used.[7],[9]
3. Blister card with multiple units: The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat–softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mould. After cooling the sheet is released from the mould and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based on the degree of protection required. Generally, the lid stock is made of aluminium foil. The material used to form the cavity is typically plastic, which can be designed to protect the dosage form from moisture.[7],[9]
4. Barrier Films: Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. Several materials may be used to provide moisture protection such as Polychlorotrifluoroethylene (PCTFE) film, and Polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapor barrier. Lack of clarity is still a drawback.[7],[9]

II. APPLICATIONS

Oral drug delivery by sublingual, mucosal and buccal be-come preferable for therapies in which immediate absorption is required including those used to manage pain, allergies, sleep problems and CNS disorders.[6]

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 tropical conditions.[9]

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 could potentially be used to treat gastrointestinal disorders.[9]

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.[1]

Vaccines:

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

1. Oral films are applicable to enhance the bioavailability of poorly bioavailable drugs.
2. Taste masking of bitter drugs.
3. Dissolvable films are loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers

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for separating multiple reagents to enable a timed reaction with a diagnostic device.[1]

Table 7: MDF Applications

Sr no	Product	Company	API	Uses
1	Klonopin wafers	Solvay Pharmaceuticals	Clonazepam (In five strengths; 0.125mg, 0.5mg, 1mg &2mg)	Anxiety
2	Listerine Cool Mint Pocket Paks	Pfizer, Inc	Cool mint	Mouth fresheners
3	Sudafed	Water-skier Health, Inc	Phenylepinephrine	Congestion
4	Suppress	Innozen, Inc	Menthol (2.5mg)	Cough suppressant
5	Triaminic	Novartis	Diphenhydramine HCL (12.5)	Anti-allergic
6	Theraflu	Novartis	Dextromethorphan HBR (15mg)	Cough suppressant
7	Benadryl	Pfizer	Diphenhydramine	Cough and allergy
8	Orafilm	Apothecus	Benzocaine	Pain relieving strips
9	Spiderman	Aquafilm	Vitamin	Vitamin supplements
10	Gas-X	Novartis	Simethicone	Anti Fluctuating
11	Chloraseptic	Prestige	Benzocaine/menthol (3mg/3mg)	Sore throat

III. CONCLUSION

Recently pharmaceutical companies embraced fast dissolving films as a practical and accepted alternative to traditional medicines. The unique properties of MDFs such as easy administration, quick disintegration, consumer preference, rapid action, etc make it a useful delivery form of medication intended for geriatric, paediatrics or dysphasic patients who have difficulty swallowing tablets and capsules. This technology is also a good tool for a pharmaceutical company for product life cycle management for increasing the patent life of existing products. These combined potentials lead to pave way for shifting primarily from OTC products to prescription products. The MDFs bridge the gap

between consumer preferences and manufacturers. Hence within the patient population and formulators, fast dissolving oral films lead to an ideal dosage form. This review is an effort to combine all the possible knowledge available on mouth-dissolving films.

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