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AN OVERVIEW OF MOUTH DISSOLVING FILMS: FORMULATION ASPECTS

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ABSTRACT

These films generally dissolve within seconds to release the active agents but can be modified to release the drug more slowly depending upon film thickness and selection of the polymer matrix. A film or strip can be defined as a dosage form that employs a water dissolving polymer which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or in the oral cavity to provide rapid local or systemic drug delivery. Upon complete disintegration, absorption of the API may occur through the buccal mucosa. Esophageal absorption may also occur during the process of swallowing saliva that contains the dissolved API. The majority of the dose ultimately ends up in the stomach and is absorbed in the GI tract in a similar manner as a traditional tablet. A traditional oral dosage form requires a fixed amount of time for stomach fluids to dissolve the entire tablet or capsule. This review article was based on the discussion of various formulation aspects of mouth dissolving films and their additives.

KEYWORDS: Mouth dissolving dosage forms (MDDF), properties, fabrication, additives.

1. INTRODUCTION

Mouth dissolving dosage forms (MDDF) have recently acquired great importance due to their properties such as quick disintegration and dissolution, obviating need of water for disintegration and especially suitable for pediatric and geriatric patients. Mouth dissolving films are the most common and widely used rapidly dissolving dosage form.[1,2]

An ideal mouth dissolving films should have following properties:

- High stability
- Transportability
- Ease of handling and administration
- No special packaging material and/or processing requirements
- No water necessary for application and pleasant taste.

Oral film strips have hit the mainstream in the last few years as a new way of freshening the breath. The wafers are slipped into the mouth and dissolve quickly to release the mint flavor.

1.1 Advantages of mouth dissolving film over mouth dissolving tablets

MDFs hold certain edges over MDTs, they are as follow.

- Despite the short disintegration/dissolution times of MDT, the fear of taking solid tablets and the risk of choking persists. [3]
- For their production, many MDT requires the expensive lyophilisation process.
- MDTs are sometimes difficult to carry, store and handle (fragility and friability).[4]
- MDTs require specialized and expensive packaging and processing.

The above mentioned limitations of MDTs have paved the way for development of MDFs as fast drug delivery systems. MDFs are gaining interest as an alternative to MDTs to definitely eliminate patients' fear of choking. MDFs are also known as fast-dispersing, mouth dissolving, orally disintegrating, fast-melting, quick dissolving films and dissolvable oral strips. [5] Initially MDFs were launched in the market as breath fresheners and personal care products such as dental care strips and soap strips. Pfizer's Warner–Lambert's created Listerine Pocket Packs as mouth freshener in 2001 and Zengen launched chloraseptic relief strip in USA, delivering Benzocaine, a local anesthetic for the treatment of sore throat. [6,7] A film or strip can be defined as a dosage form that employs a water-

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dissolving polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly hydrate, adhere, and dissolve to release the drug when placed on the tongue or in the oral cavity.[8,9]

MDFs can provide a convenient and effective way for delivering active ingredients such as pharmaceutical compounds and breath freshening agents, to the mucosa of humans and animals.[10] It allows the drug to be delivered to the blood stream either intragastrically, buccally or sublingually.[11]

When MDFs are administered, rapid absorption of drug, through the sublingual route is possible, which finally leads to quick onset of drug action. The proper selection of incorporated excipients/ ingredients for formulating MDF is very important as MDF have to disintegrate and/or dissolve quickly into the oral cavity. Besides water-dissolving polymer, the formulation may include other components depending on its intended use.[12]

The product attributes that a patient today seeks in a dosage form are-

- Better portability
- Ease and accuracy of dosing
- Overall convenience

MDF are already being used in breath freshening product introductions from Warner Lambert and Wrigley's in the USA and Europe, and Boots in the UK, as well as vitamin products. Consumers have now been exposed to this concept through the introduction of multiple breath-freshening products introduced over the past 2 years, and the trend is now towards developing over the counter (OTC) and prescription products in this delivery form. The delivery system is simply placed on a 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 oramucosal absorption or, with formula modifications, will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed.[13-22]

1.2 Advantages and disadvantages of mouth dissolving films

Advantages

1. The film diminishes fear of throat choking.
2. The film is easy to handle and administer.
3. The film requires a simple and convenient packaging.
4. The film masks unpleasant taste and is easy to manufacturer.
5. This system allows children, elderly and the general population to take their medication directly wherever and whenever needed.
6. The Mouth dissolving action is primarily due to the large surface area of the film.
7. The films are tough, solid, soft, flexible and do not require special packaging.
8. The films are thin and can be carried in a patients pocket and wallet.
9. The films enhance stability of some formulations.

Disadvantages

1. The major disadvantage of MDFs is that high dose cannot be incorporated into the film. However, research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip. [23] There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose APIs. As an example of this, Labtec claim that the Rapid Film technology can accommodate dose of up to 30 mg. This clearly limits the range of compatible drug products.
2. The other technical challenge with these dosage forms is achieving content Uniformity.[24]

The key advantage for rapidly dissolving film is patient compliance and convenience. The main drawback is with drug loading. Drug loading is generally limited to roughly 20mg. This problem can be addressed by increasing the thickness of the strip, but that in turn may change the dosage form to slowly dissolving film. But drug companies have been interested in this technology as it provides fast, accurate dosing that is expected to increase compliance, particularly among children. There is no need for water or measuring, and upon melting, the dose of medicine is swallowed. The likely candidates for rapidly dissolving films or oral thin films are nicotine replacing its transdermal delivery, antiulcer drug and antihistamine products. Prescription products, antipsychotic and sleeping disorder drugs are the potential candidates.[13-22]

Literature survey suggest that MDFs consists of APIs, antimicrobial agents, nutraceutical ingredients, plasticizers, surfactants, colorants, sweetening agents, saliva stimulating agents, flavors, flavor enhancers and other excipients.

A typical composition of MDFs contains the following excipients:

Table 1: Composition of MDFs

Components	Quantities (%)
Drug	1 – 25
Water-soluble polymers	40 – 50
Plasticizers	0 – 20
Fillers, colour, flavour etc	0 – 40

As polymers and plasticizers form the main body of MDFs, therefore, their properties greatly affect the characteristics of MDFs.

1.3 Components of MDFs formulation

Formulation of MDFs involves the intricate application of aesthetic and performance characteristics such as taste masking, Mouth Dissolving, physical appearance, mouth-feel etc. The excipients used in formulation of MDFs are given below as per their categories. For the regulatory perspectives, all excipients used in the formulation of MDFs should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

1.3.1 Film formers

A variety of polymers are available for preparation of MDFs. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation.[39] On the other hand, Mouth Dissolving strip dosage form should have the property to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously. Lists of polymers which are used in oral strip are given in Table.

Table 2: List of polymers used in MDFs formulation

Natural gums	Pullulan gum, Locust bean gum, Carrageenan gum, Xanthan gum,Guar gum
Synthetic polymers	Polyvinyl pyrrolidone (PVP), Sodium carboxy methyl cellulose, Gelatin, Hydroxyl propyl methyl cellulose, Methocel™ E3, E5, E15, E50 and K3, Polyethylene oxide, Polyox™ N10, N80 and N750

1.3.2 Plasticizers

Plasticizer is a vital ingredient of the MDFs formulation. It helps to improve the flexibility of the strip and reduce the brittleness of the films. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer.[25,26] 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 are some of the commonly used plasticizer excipients.

However inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip.[27] It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.[28] The plasticizer employed should impart the permanent flexibility to the strip and it depends on the volatile nature of plasticizer and the type of interaction with the polymer. It should be noted that the properties of plasticizer are important to decrease the glass transition temperature of polymer in the range of 40 - 60 ºC for non aqueous solvent system and below 75 ºC for aqueous systems.[29] Plasticizer should be compatible with drug as well as other excipients used for preparation of strip.[25] Cellulosic hydrophilic polymers were easily plasticized with hydroxyl containing plasticizers like PEG, propylene glycol, glycerol and polyols. In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid.[30] Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both hypromellose as well as polyvinyl alcohol films.[25]

1.3.3 Active pharmaceutical ingredients

The market for thin film (strips) is mainly for the vitamins, minerals and supplements (VMS) and OTC areas. Active ingredients which appear to be suitable are vitamins, supplements such as melatonin and Coenzyme Q10 (CoQ10), and some OTC ingredients. Examples of the type of developments in this area are deals between Bioenvelop and NutriCorp, who have approval for a range of products in Canada including benzocaine, caffeine and menthol. To give another example,

Leiner Health Products have an exclusive deal to sell MonoSol film strips for OTC products, the first of which is reported as a melatonin supplement.[31] A class of molecules that can be incorporated into this delivery system, includes cough/cold remedies (antitussives, expectorants), sore throat, erectile dysfunction drugs, antihistamines, antiasthmatics, gastrointestinal disorders, nausea, pain, CNS drugs (Anti-Parkinson), caffeine strips, snoring aid, multivitamins, sleeping aid etc. The MDFs technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in MDFs. Generally 5 % w/w to 30 % w/w of active pharmaceutical ingredients can be incorporated in the MDFs. Multivitamins up to 10 % w/w of dry film weight was incorporated in the MDFs with dissolution time of less than 60s.[32] While water soluble APIs are present in the dissolved state in the MDFs or in the solid solution form, the water insoluble drugs are dispersed uniformly in the strip. The distribution of water insoluble molecules in water miscible polymer becomes important for the large scale manufacture point of view. Many APIs, which are potential candidates for MDFs technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the MDFs, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation.[33] The MDFs technology offers advantages in certain critical clinical situations. For drugs that are projected as local anesthetic or pain killer, the MDFs has demonstrated improved clinical benefits. Certain pathologies require instantaneous release of the medicament for prompt relief. For instance, in the case of migraine a rapid clinical effect is desired by the individual. Regiospecific delivery of the medicament would be required in the cases of sore throat, cough, allergy and other local oral manifestations. This dosage form can also be used for natural extracts and neutraceuticals including vitamin B_{12}, chromium picolinate, melatonin and possibly CoQ10.[34] Some of the examples of reported suitable drug molecules that can be incorporated in the MDFs are listed in following Table.[35]

Table 3: Suitable candidates for Mouth Dissolving Films

Molecule	Therapeutic category	Dose
Nicotine	Smoking Cessation	1.0–15.0 mg
Nitroglycerin derivatives	Vasodilator	0.3–0.6 mg
Zolmitriptan	Anti migraine	2.5 mg
Loratidine	Antihistaminic	5–10 mg
Desloratidine	Antihistaminic	5.0 mg
Diphenhydramine hydrochloride	Antihistaminic	25.0 mg
Loperamide	Antidiarroheal	2.0 mg
Famotidine	Antacid	10.0 mg
Flurazepam Anxiolytic	Anticonvulsant	15.0–30.0 mg
Chlorpherinamine maleate	Antihistaminic	4.0 mg
Acrivastine	Antihistaminic	8.0 mg
Oxycodone Opoid	Analgesic	2.5–10.0 mg
Diclyclomine	Muscle Relaxant	25.0 mg
Omeprazole	Proton pump inhibitor	10.0–20.0 mg
Cetrizine	Antihistaminic	5.0–10.0 mg
Ketoprofen	Anti–inflammatory	12.5–25.0 mg
Azatidine maleate	Antihistaminic	1.0 mg
Sumatriptan succinate	Antimigraine	35.0–70.0 mg
Chlorhexidine gluconate	Antimicrobial	0.12%
Tiprolidine hydrochloride	Antihistaminic	2.50 mg
Ondansetron hydrochloride	Antiemetic	4-8 mg
Prochlorperazine	Antiemetic	5 mg
Levocetirizine	Antihistaminic	5 mg

1.3.4 Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. Suitable sweeteners include:

- Water soluble natural sweetener: Xylose, ribose, glucose,sucrose, maltose, stevioside etc.
- Water soluble artificial sweetener: Sodium or calcium saccharin salts, cyclamate salts, acesulfame-k etc.
- Dipeptide based sweetener: Aspartame.
- Protein based sweeteners: Thaumatin I and II.

The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation.[36] Aspartame was used for the preparation of oral strips of valdecoxib.[37] For the oral strip of piroxicam, maltodextrin was employed as sweetening agent.[38] Generally sweeteners are used in the concentration of 3 to 6 % w/w either alone or in combination.[36]

1.3.5 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 rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized 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 % w/w of weight of the strip.[38] Other ingredients should be incorporated like sweetening agents, flavouring agents, coloring agents, stabilizing and thickening agents. Some time surfactant and emulsifying agents are also added in very minute quantity to manipulate film properties.

1.4 Manufacturing flexibilities of dissolvable film technology

In addition to the potential to deliver many different types of APIs, the primary benefit of dissolvable film technology to pharmaceutical manufacturers is the flexibility of the film manufacturing. Dissolution rate, materials selection, and the rate of absorption can be controlled. Precision manufacturing capabilities provide manufacturers an advantage in bringing a new product or extension of an existing product to market.

1.4.1 Dissolution rate

Oral thin films are capable of more than just the immediate release of APIs, as demonstrated by the existing products currently on the market. The film technology can be customized for controlled oral dissolution that ranges from seconds to hours. Particular attention to the selection of excipients is the key to develop a thin film (oral dosage form) that may disintegrate very rapidly for immediate-release applications or that may disintegrate slowly for controlled-release applications.

1.4.2 Materials selection

Film technology offers an unlimited set of raw materials to pharmaceutical companies for delivering APIs. These materials include traditional aqueous-soluble as well as non-aqueous-soluble ingredients.[39] Dispersion of a non-soluble API may be prepared in film form. The dispersed phase within the bulk fluid must remain uniform throughout the film manufacturing process to prevent segregation of the API. Fluid rheology is an important consideration for assurance that the dispersed phase remains suspended. Established and effective taste-masking approaches used to formulate APIs in syrups and soft-chew dosage forms can be applied to APIs in the thin film oral dosage format. Successful taste-masking methods that have been used include traditional flavor and sweetener combinations, encapsulation, or particle coating, and complexation with ion exchange resin.[40] It is important to consider and recognize any taste-masking techniques that result in discrete particles. Particle size is a critical factor in the manufacturing process and depends on the coating method selected. Generally, particles larger than 250 microns could present problems for some coating techniques if they accumulate in the fluid flow path, which could cause scratches on the surface of thin coating layers.

1.4.3 Manufacturing

The manufacturing of MDFs involves numbers of steps. It is a precise process that controls the functional properties of the films: thickness, width, drug concentration, residual volatiles, tensile strength, and disintegration rate. Within the various steps of the manufacturing process, the coating process is the key to the successful development of MDFs. Multiple techniques, such as liquid casting or 100 % solids extrusion, are used to create thin films. The manufacturing process for MDFs is based on existing manufacturing techniques, such as transdermal drug delivery systems. This is important because of the need to hold tight tolerances of the film when manufacturing products with highly potent compounds and APIs with a narrow therapeutic index in order to produce a uniform pharmaceutical product with low variability within a thin film.

1.4.4 Absorption profile/rate

Unlike traditional oral dosage forms, an MDF is completely dissolved in the oral cavity and therefore, the entire API payload is immediately available in stomach for absorption to the systemic circulation. In terms of bioavailability, the area under curve (AUC) for a MDF versus an oral tablet or capsule may remain unchanged; however, Tmax may be shorter. There are certain medical disorders in which an earlier therapeutic effect may be warranted and advantageous. MDFs are compatible with microspheres and other specialized release technologies. Dissolvable films may also offer expanded bioavailability potential versus other delivery methods. The chemistry of MDFs may enhance specific API uptake, depending upon the properties of API. The format allows for the ability to load as much as 50 mg or more of a single API or combination of APIs.

Table 4: List of marketed products [38]

Product category	Ingredients	Application
Biofilm		
Energy boosters	Caffeine, green tea extract and guarana	The product maintains the energy levels.
Detoxification strip	Green tea extract which is high in polythenols and rich in anti-oxidants. Spearmint flavor.	Green tea has been used as a traditional medicine to help everything from wound healing, regulating body temp., blood sugar and promoting a healthy digestion
Male vitality strip	Maca root extract and Siberian ginseng extract, herbs which enhance libido, Cinnamint flavor.	It acts as an aphrodisiac and improves the libido in males.
Female vitality strip	Botanical ingredients like damiana and passion flower	It is used to improve general well-being, increase energy and enhance mood
Appetite suppressant	Fucus vesiculosus and guarana extract, garcinia cambogia	These are top selling natural ingredients associated with weight loss. Cambogia helps to reduce the food intake by suppressing appetite.
Vitamins and food supplements	Various vitamins, minerals and supplements	It is useful for the people who do not like to pop up the tablets or soluble supplements
Breath freshener strip, (Antibacterial strip)	Contain mint flavor and antibacterial agent, cetylpyridinium chloride	It is used as mouth freshener and to stop bad breath.
Saliva promoting strips	Fruit acid extracts, range of flavors	It is used in the dry mouth as a side effect of the other medications.

Product category	Ingredients	Application
Labtec GmbH		
Ondansetron Rapidfilm®	Ondansetron 4 mg and 8 mg.	It is used in the prevention of chemotherapy and radiation-induced nausea and vomiting and prevention of postoperative nausea and vomiting.
Donezepil Rapidfilm®	Donepezil Hydrochloride 5 mg and 10 mg.	Treatment of mild to moderately severe dementia of the Alzheimer's type.
Paladin Labs (Bioenvelop)		
Smoking cessation	Nicotine	To reduce the smoking habit
Multivitamin for kids and adults	B6, B12, C; D3 for kids, D3 for adults	Multi vitamin supplement,
Teeth whitening	-	Lifestyle improvement product
Food supplements	Benzocaine, Caffeine, Melatonin, MentholOmega, Hoodia, Protein, Vinpocetine	Nutraceuticals
Minerals	Chromium	Mineral supplements
Natural products	Ginseng, Guarana	Aphrodisiac, Appetite reducer.
Innozen Inc		
Chloraseptic® Relief Strips™	Benzocaine 3 mg, BHT, corn starch, erythritol, FD&C Red 40, hydroxypropyl methylcellulose, malic acid, menthol, monoammonium glycyrrhizinate, cherry flavors, polyethylene oxide, sucralose	Occasional minor irritation, pain, sore throat and sore mouth
Chloraseptic® Kids Sore Throat Relief Strips	Benzocaine 2 mg and menthol, grape flavor, BHT, cornstarch, erythritol, FD&C Blue 1, FD&C Red 40, hydroxypropyl methylcellulose, malic acid, menthol, monoammonium glycyrrhizinate, polyethylene oxide, sucralose	Occasional minor irritation, pain, sore throat and sore mouth
Suppress™ Cough strips with Dextromethorphan	Dextromethorphan hydrobromide 2.5 mg, Asulfame potassium, FD&C Blue 1, glycerin, menthol, natural and artificial flavors, pectin, peppermint oil, sucralose, sugar, water	Temporarily suppresses coughs due to minor throat and bronchial irritation associated with cold or inhaled irritants.

Product category	Ingredients	Application
Suppress™ Cough strips with menthol	Artificial flavors, ascorbic acid, aspartame, asulfame potassium, carrageenan, diglycerides, fatty acid ester, FD&C yellow 5 (tartrazine), glycerin, menthol, monoglycerides, pectin, sodium alginate, sorbitan monolaurate, sorbitol, spices, starch, water	Temporarily suppresses coughs due to minor throat and bronchial irritation associated with cold or inhaled irritants.
Hughes Medical Corporation		
Methylcobalamin	1 mg	Peripheral neuropathy, Diabetic neuropathy
Dextromethorphan	2.5 mg–5.5 mg–15 mg	Anti-tussive agent used to prevent cough.
Folic Acid	1 mg–5 mg	Required for formation of healthy red blood cells and used in anemia.
Loratidine	10 mg–20 mg	It is a non sedative antihistaminic agent used to treat the allergy.
Caffeine	2.5 mg	It is used as a stimulant
Diphenhydramine HCl	2.5 mg–5 mg	It is used as antihistaminic, sedative, hypnotic and antiemetic
Novartis Pharmaceuticals		
Night Time Triaminic Thin Strips® Cold & Cough	Diphenhydramine HCl 12.5 mg, Phenylephrine HCl 5 mg, acetone, FD&C blue #1, FD&C red #40, flavors, hypromellose, maltodextrin, mannitol, polyethylene glycol, polypropylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide.	Antihistamine/cough suppressant, Nasal decongestant. It temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold. Nasal and sinus congestion. Itchy and runny nose
Triaminic Thin Strips® Long Acting Cough	Dextromethorphan 5.5 mg (equivalent to 7.5 mg Dextromethorphan HBr), acetone, alcohol, dibasic sodium phosphate, FD&C red # 40, flavors, hydroxypropyl cellulose, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, polacrilin, polyethylene glycol, pregelatinized starch, propylene glycol, purified water, sodium phosphate, sorbitol, sucralose, titanium dioxide.	It temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold.

Product category	Ingredients	Application
Triaminic Thin Strips® Cough & Runny Nose	Diphenhydramine HCl 12.5 mg, acetone, alcohol, FD&C blue # 1, FD&C red # 40, flavors, hydroxypropyl cellulose, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, purified water, sodium polystyrene sulfonate, sorbitol, sucralose, titanium dioxide	It reduces cough due to minor throat and bronchial irritation as may occur with a cold. It relieves itchy, watery eyes due to hay fever.
Day Time Triaminic Thin Strips® Cold & Cough	Dextromethorphan 3.67 mg (equivalent to 5 mg Dextromethorphan HBr), Phenylephrine HCl 2.5 mg, acetone, alcohol, FD&C blue #1, FD&C red #40, flavors, hypromellose, isopropyl alcohol, microcrystalline cellulose, polacrilin, polyethylene glycol, propylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide	It is used as nasal decongestant.
Triaminic Thin Strips® Cold with Stuffy Nose	Phenylephrine HCl 2.5 mg, acetone, alcohol, FD & C blue #1, FD&C red # 40, flavors, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, polyethylene glycol, propylene glycol, purified water, sodium polystyrene sulfonate, sucralose and titanium dioxide	It temporarily relieves nasal and sinus congestion as may occur with a cold.
Theraflu® Daytime Thin Strips	Dextromethorphan 14.8 mg (equivalent to 20 mg Dextromethorphan HBr), Phenylephrine HCl 10 mg, acetone, alcohol, FD&C red #40, flavors, Hypromellose, mannitol, polyethylene glycol, polystyrene sulfonate, polacrilin and sucralose	It temporarily relieves nasal and sinus congestion as may occur with a cold. It reduces cough due to minor throat and bronchial irritation as may occur with a cold.
Theraflu® Nighttime Thin Strips	Diphenhydramine HCl 25 mg, Phenylephrine HCl 10 mg, acetone, alcohol, FD&C blue #1, flavors, Hypromellose, mannitol, polyethylene glycol, polystyrene sulfonate, polacrilin and sucralose	glycol, polystyrene sulfonate, polacrilin and sucralose. It is used for nasal congestion, runny nose, sneezing, itchy nose and throat etc.

Product category	Ingredients	Application
Theraflu® Thin Strips®–Multi Symptom	Diphenhydramine HCl 25 mg, acetone, alcohol, FD&C red #40, flavors, Hypromellose, hydroxyl propyl cellulose, maltodextrin, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, polystyrene sulfonate, sorbitol and sucralose. Titanium dioxide.	It temporarily relieves nasal and sinus congestion as may occur with a cold. It reduces cough due to minor throat and bronchial irritation as may occur with a cold.
Pfizer Inc		
Listerine® pocketpaks®	Available in cool mint®, Fresh Citrus, Cinnamon, and fresh burst®. Pullulan is used as a film forming polymer.	These strips dissolve instantly and kill 99% of bad breath germs.
Prestige Brands		
Little cold sore throat strip	Ascorbic acid, pectin	Cold/allergy
Chloraseptic relief strip	Chloraseptic relief strip	Sore throat
BioDelivery Sciences International		
Onsolis™	Fentanyl buccal soluble film	Pain in opioid-tolerant patients
BEMA™ Buprenorphine	Buprenorphine	Therapeutic alternative for patients with incomplete pain relief or those unable to tolerate the side effects of non-narcotic analgesics
MonoSolRx		
Pedia-lax Quick Dissolving Strips	Sennoside A&B 8.6 mg	Cardiac glycosides
Store brand cough suppressant Medicated strips	Dextromethorphan HBr 7.5 mg / 15 mg	It temporarily relieves nasal and sinus congestion as may occur with a cold. It reduces cough due to minor throat and bronchial irritation as may occur with a cold.

2. Review of literature

2.1 Review of literature related to mouth dissolving film

Mishra et al. (2011) prepared and evaluated the rapidly dissolving films of cetirizine hydrochloride using pullulan as film forming polymer. Pullulan is a water soluble polysaccharide produced from yeast *Aureobasidium pullulans*. Cetirizine hydrochloride, an antihistamine drug was selected for the study. Solvent casting was the method used for formation of rapidly dissolving films. The films exhibited satisfactory thickness, mechanical properties like tensile strength, % elongation and elastic modulus. *In vitro* dissolution studies, *in vivo* disintegration studies and surface morphology using environment scanning electron microscopy were also performed. Surface morphology study suggested even distribution of cetirizine hydrochloride in the film and uniformity of the film. The optimized batch was found to be stable for six months under specified stability conditions. [41] **Cilurzo et al. (2010)** developed a fast-dissolving film made of low dextrose equivalent maltodextrins (MDX)

containing nicotine hydrogen tartrate salt (NHT). Particular attention was given to the selection of the suitable taste-masking agent (TMA) and the characterization of the ductility and flexibility under different mechanical stresses. The bitterness and astringency intensity of NHT and the suppression effect of several TMA were evaluated by a Taste-Sensing System. As expected, placebo films made of MDX DE 6 appeared stiffer and less ductile than film prepared using MDX DE 12. The films disintegrated within 10s. Among the tested TMA, the milk and mint flavours resulted particularly suitable to mask the taste of NHT. The addition of NHT and taste-masking agents affected film tensile properties. The feasibility of NHT loaded fast dissolving films was demonstrated.[42] **Kunte et al. (2010)** investigated the possibility of developing verapamil fast dissolving strips. The strips were prepared by solvent casting method with of HPMC E6 and maltodextrin. The strips were evaluated for drug content uniformity, thickness, folding endurance, in vitro disintegration time, in vitro dissolution, surface pH and palatability. Disintegration time showed by formulation was found to be in range of 21-29 sec. Formulation containing 2 % HPMC E6 and 3.5% w/v maltodextrin showed satisfactory results against other formulations. They have concluded that fast dissolving strips of verapamil can be prepared for better patient compliance and effective therapy.[43] **Sudeendra et al. (2010)** designed and optimized bioadhesive vaginal films of clotrimazole that could be retained in the vagina for prolonged period for more effective treatment against vaginal candidiasis. Bioadhesive films were formulated by solvent casting technique using bioadhesive polymers such as chitosan, HPMC and sodium CMC. Glycerin and PEG-400 were used as plasticizer. The films were characterized for various physical, mechanical, and aesthetic properties. Bioadhesive strength, antifungal activity and *in vitro* release studies suggested that the prolonged release bioadhesive vaginal film formulation of clotrimazole is useful and effective dosage form for treating vaginal candidiasis.[44] **Dixit et al. (2009)** explained that over the recent past, many of the research groups are focusing their research on this technology. Amongst the plethora of avenues explored for rapid drug releasing products, Oral strip technology (OST) is gaining much attention. The advantages of OST are the administration to pediatric and geriatric patient population where the difficulty of swallowing larger oral dosage forms is eliminated. This technology has been used for local action, rapid release products and for buccoadhesive systems that are retained for longer period in the oral cavity to release drug in controlled fashion. OST offers an alternate platform for molecules that undergo first pass metabolism and for delivery of peptides. The review article is an overview of OST encompassing materials used in OST, critical manufacturing aspects, applications, commercial technologies and future business prospects of this technology.[45] **Gohel et al. (2009)** prepared fast dissolving films of salbutamol sulphate using HPMC, PVP and polyvinyl alcohol by applying experimental design technique. Simple lattice design and desirability function were adopted for the preparation of film possessing desirable and optimized characteristics. The polymer greatly influenced the mechanical properties and % drug release from the film. From the computed value of desirability function, it was determined that the film containing HPMC and polyvinyl alcohol was the best batch. The experimental design serves to be a useful tool for the formulation development of mouth dissolving film.[46] **Dahiya et al. (2009)** said that the ultimate goal of any drug delivery system is the successful delivery of the drug to the body; however, patient compliance must not be overlooked. Fast dissolving drug delivery systems, such as, mouth dissolving films (MDF), offer a convenient way of dosing medications, not only to special population groups with swallowing difficulties such as children and the elderly, but also to the general population. MDF are the novel dosage forms that disintegrate and dissolve within the oral cavity. Intra-oral absorption permits rapid onset of action and helps in avoiding the first-pass effects, thereby reducing the unit dose required to produce desired therapeutic effect. The present review provides an overview of various polymers that can be employed in the manufacture of MDF and highlights the effect of polymers and plasticizers on various physico-mechanical properties of MDF. It further gives a brief account of formulation of MDF and problems faced during its manufacture.[47] **Chen et al. (2008)** investigated fast dissolving and extended release edible films for dissolution time, release profiles and film strength. Benzocaine, caffeine, lidocaine and diphenylhydramine were used as a model drugs. Various film forming polymers were employed in the study namely hydroxypropyl methylcellulose, methylcellulose and polyethylene oxide. The disintegration and dissolution time of the films reflected the fast dissolving and extended release applications which depended on the nature of film forming polymers. Four different systems

were prepared and evaluated. The first and second systems were edible films containing polymers, plasticizers, benzocaine or caffeine along with other excipients. Third system was a buccal film delivery system. Fourth system included cold pack and wound dressing products. As the film thickness increased, the disintegration and dissolution time increased. However, at same thickness, higher loading of the API decreased the disintegration and dissolution time of the films. The puncture strength of HPMC E series increased when molecular weight of the polymer increased. The mechanical strength of polyox (PEO) films also showed similar observations. The puncture strength of PEO is much lower than that of cellulose based methyl cellulose and HPMC polymers.[48] **Cilurzo et al. (2008)** studied maltodextrins with a low dextrose equivalent as a film forming material and its application in the design of fast dissolving films of piroxicam. The effect of plasticizer concentration was studied on the mechanical property of the film. Flexible films were obtained by using 16-20 % w/w glycerin. Casting, solvent evaporation and hot melt extrusion were used as production technologies by adding sorbitan monooleate and microcrystalline cellulose respectively. It was observed that microcrystalline cellulose decreased film ductility and affected in-vitro and in-vivo film disintegration. The films exhibited a high loading capacity up to 25 mg per 6 cm2 of surface. The dissolution rate of piroxicam was significantly improved in films prepared by casting and solvent evaporation independently of piroxicam to maltodextrin ratio.[49] **Okabe et al. (2008)** developed an easily swallowed film formulation that swells and turns into a jelly instantaneously upon absorption of a small amount of saliva. The formulation's structure comprises a gelating layer on both faces of a drug-containing layer, and this structure restrains the elution of a drug in the mouth. Swelling experiments confirmed the instantaneous gelation when the gelating layer absorbs purified water. Fifteen seconds after immersion in purified water, the bulk modulus of the film formulation was less than 500 N/m^2, which is an appropriate value for easy swallowing by elderly people. A dissolution study confirmed the delayed dissolution of glimepiride as a model drug. In a clinical study, although the stagnation at the upper esophagus was observed with a gelatin capsule, the film formulation passed the esophagus and reached the stomach quickly.[50] **Dinge et al. (2008)** investigated formulation of triclosan (TC) containing fast dissolving films for local delivery to oral cavity. Various film forming agents, film modifiers and polyhydric alcohols were evaluated for optimizing the composition of fast dissolving films. The potential of poloxamer 407 and hydroxypropyl-beta- cyclodextrin (HPBCD) to improve solubility of TC was investigated. Fast dissolving films containing hydroxypropyl methylcellulose (HPMC), xanthan gum, and xylitol were formulated. Use of poloxamer 407 and HPBCD resulted in significant improvement in the solubility of TC. Films containing TC-poloxamer 407 exhibited better in vitro dissolution profile and in vitro antimicrobial activity as compared to films containing TC-HPBCD complex.[51] **Barnhart et al. (2007)** explained dissolvable oral thin films (OTFs) are a proven technology for the systemic delivery of active pharmaceutical ingredients (APIs). Pharmaceutical companies and consumers, particularly pediatric and geriatric patient populations, have adopted OTFs as a practical alternative to traditional OTC medicines, such as liquids, tablets, and capsules, because of the various benefits of the films (fast, accurate dosing; safe, efficacious format; convenience; portability). The next generation of dissolvable films is being designed to move beyond immediate-release oral delivery into applications such as implantable, topical, sublingual, and gastro-retentive platforms for the delivery of both small and large molecules. This work is the direct result of the flexibility in dissolvable film design and manufacture. This article attempts to outline the next generation of films, the benefits of the platform across delivery routes, and the primary considerations in formulating for novel applications.[52] **Ali et al. (2007)** examined high molecular weight povidone K-90 polymer as a film forming excipient for fast dissolving drug delivery applications. It was evaluated in combination with povidone K-30 and other kollidon SR polymers. Fast dissolving films suitable for delivery of highly potent drugs and vitamins could be formulated using the polymer povidone K 90 with auxiliary polymers. K-90 films with increased amount of polyvinyl acetate and acrylic acid based kollidon SR and MAE 100P respectively showed significant flexibility and elongation. Increased amount of K-30 and kollidon VA 64 showed good flexibility. All films were highly hydrophilic and dissolved in 60 s or less except K90/kollicoat MAE 100P which dissolves in 6-7 min.[53] **David et al. (2007)** studied the mechanical and calorimetric properties of acid hydrolyzed hydroxyl propylated pea starch (HPPS) and k-carrageenan films. The mixture was prepared by mixing HPPS (25%, w/w), an easily slurried non-

gelling polysaccharide, and a k-carrageenan (61% w/w) used for its gelling properties. Compared to individual components, the rheological properties of the hot mixtures at 60 °C showed a dramatic increase of the viscosity. Overall, the final film properties of the blends were similar to those of the films with starch alone. This means that the influence of the k-carrageenan on the solid-state behaviour of the blends was hidden, in spite of the strong influence of k-carrageenan on the rheological behaviour in the solution and in the gel state.[54] **Chen et al. (2006)** formulated fast dissolving films using water soluble polymers for achieving rapid disintegration, good mouth feel and mechanical properties. Desired fast disintegration and mechanical properties could be tailored with polyethylene oxide and HPMC. Films had good mouth feel and no sticky feeling. Film strength of films containing PEO and HPMC ranged between 3000 kg/m2 to 17000 kg/m2. Increase in glycerin content resulted in marked decrease in film strength.[55] **Onishi et al. (2005)** developed novel mucoadhesive patch of diazepam to achieve its rapid absorption for the emergency treatment of epileptic seizure or anxiety disorder. The patch consisted of outer mucoadhesive region of carbopol 934, central drug region and tegaderm as backing layer. Diazepam was dissolved in propylene glycol alone or propylene glycol containing oleic acid at 5.6%w/w.[56] **Siemann et al. (2005)** said that nowadays, the solvent cast technology is becoming increasingly attractive for the production of films with extremely high quality requirements. The advantages of this technology include uniform thickness distribution, maximum optical purity and extremely low haze. The optical orientation is virtually isotropic and the films have excellent flatness and dimensional stability. The cast film can be processed in-line with an optical coating design.[57] **Mashru et al. (2005)** prepared fast dissolving films for sublingual route containing salbutamol sulphate and polyvinyl alcohol as polymer. The films were evaluated for mechanical properties, in vitro release study and morphology study. A 33 factorial design was applied to study the effect of polyvinyl alcohol, glycerin and mannitol on % drug release and mechanical properties of the films. It was observed that polyvinyl alcohol had positive effect on tensile strength and mannitol had negative effect on tensile strength. Mannitol produced positive effect on drug release where as polyvinyl alcohol produced negative effect on drug release.[58] **Repka et al. (2003)** studied that hot-melt extrusion technology (HME) was used to prepare muco-adhesive matrix films containing 10 % w/w clotrimazole (CT) intended for local drug delivery applications for the oral cavity. This study was aimed at the production and characterization of these drug delivery systems for the prophylaxis and treatment of oral candidiasis.[59] **Honary et al. (2002)** studied effect of different molecular weights and concentration of PEG as plasticizer in HPMC films. Thermomechanical and mechanical properties of the cast films were tested using tensile and dynamic mechanical thermal analysis testing. Addition of plasticizer decreased both properties. Lower grades of PEG i.e. 300, 400 and 600 had more effect than higher molecular weights and concentrations. Glass transition temperature (Tg) decreased as molecular weight of PEG decreased and this effect was more pronounced for lower molecular weight than higher molecular weight PEG. Effect of molecular weight was much higher than effect of concentration of PEG.[60]

2.2 Review of literature related to drug and excipients

Choudhary et al. (2011) studied the film forming properties of various film formers used in oral film technology. Different grades of methocel, polyox and natural gums were used as film formers. Films were prepared by solvent casting method. Films composed of pullulan in combination with xanthan gum showed excellent film forming capacity along with tensile strength 5.56 N/mm^2, disintegration time 22 sec and dissolution time 42 sec.[61] **Kanakadurga devi et al. (2010)** Formulated and evaluated oral disintegrating tablets of montelukast sodium and studied the effect of functionality of superdisintegrants. They prepared fast disintegrating tablets of Montelukast sodium for enhanced dissolution rate. The tablets were prepared with three superdisintegrants i.e. polyplasdone XL10, Ac-Di-Sol and Primojel. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, Compressibility index and Haussner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 9sec. Based on dissolution rate the disintegrants can be rated as Polyplasdone XL10 > Ac-di-sol > Primojel. Hence polyplasdone XL10 was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of Montelukast sodium. All the dissolution parameters were calculated and compared with

market tablet. An increase in the dissolution rate was observed with M8 formulation when compared to market one. It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using super disintegrants.[62] **Verena et al. (2010)** compared different film forming materials used for the preparation of fast dissolving oral film. Caffeine was used as model drug. Films were prepared with by slide frame method and petridish method. All films were dissolved within 40 sec. drug loaded films disintegrated more slowly than the drug free formulation. Disintegration / dissolution was fastest with film made from the carboxy methyl cellulose (CMC). Dissolution times for drug loaded oral films made from CMC and HPMC differed significantly. They concluded that film with HPMC was the most suitable film-forming materials for drug- free and caffeine-loaded film, providing fast dissolution films that were not sticky and were easy to handle.[63] **Murata et al. (2010)** explained that fast-dissolving films (FDFs) were prepared from natural polysaccharides, such as pullulan, without heating, controlling the pH, or adding other materials. The release profiles of model drugs from the films were investigated. In the absence of a drug, the casting method and subsequent evaporation of the solvent resulted in the polysaccharide forming a circular film. The presence of drugs (both their type and concentration) affected film formation. The thickness of the film was controllable by adjusting the concentration of the polysaccharide, and regular unevenness was observed on the surface of 2% pullulan film. All films prepared with polysaccharides readily swelled in dissolution medium, released the incorporated compound, and subsequently disintegrated. The release of dexamethasone from the films was complete after 15 min, although this release rate was slightly slower than that of pilocarpine or lidocaine. Therefore, FDFs prepared from polysaccharides could be promising candidates as oral dosage forms containing drugs, and would be expected to show drug dissolution in the oral cavity.[64] **Kulkarni et al. (2010)** explored the different polymers for use in the formulation of fast dissolving strips. The films were prepared by solvent casting method. Prepared strips were evaluated for film forming capacity, visual appearance and disintegration time. The different polymers were explored for the formulation of strip such as HPMC E15, HPMC K4M, HPMC E5, PVA, PVP, gelatin, Eudragit RL100, and pullulan with different excipients such as carrageenan, guar gum. PEG 400, glycerin. Among all polymers pullulan and HPMC E15 were showed desired film forming capacity. Although the disintegration time of tablets and capsules can be determined using the test provided by USP. In this study, the dissolution rates based on disintegration and total dissolution time of the oral films were determined by mouth and by visual method.[65] **Janugade et al. (2009)** prepared an oral press-coated tablet was using direct compression and wet granulation methods to achieve the predetermined lag time. This press-coated tablet containing montelukast sodium in the inner core was formulated with an outer barrier layer by different compositions of hydrophobic polymer ethylcellulose and hydrophilic polymer low-substituted hydroxypropylcellulose. The effect of formulation composition on the barrier layer comprising both hydrophobic and hydrophilic excipients on the lag time of drug release was investigated. It was observed that lag time decreases with increasing concentration of low-substituted hydroxypropylcellulose. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time.[66] **Saravanan et al. (2008)** explained Identification, synthesis, isolation and spectral characterization of potential impurities of montelukast sodium. During the process development of montelukast sodium, three polar impurities and one non-polar impurity with respect to montelukast sodium were detected by simple reverse phase high-performance liquid chromatography (HPLC). Initially, all the four impurities were identified by the liquid chromatography–mass spectrometry (LC–MS) data and out of four impurities, three have been prepared by the synthetic method and remaining one is isolated by preparative HPLC. Based on the spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS), the structure of these impurities were characterized.[67] **Ming et al. (2007)** said that commercial oral pharmaceutical film products have been used for sore throats, cough suppression, and vitamin supplements. Retail sales of these types of edible films are expected to reach at least $350 million by 2008. In this study, drug delivery via fast dissolving and extended release edible films was investigated for dissolution time, release pro-files, and film strength. Three film delivery systems were evaluated to determine acceptable levels of benzocaine where the active pharmaceutical ingredient (API) would not bloom to the surface of

the film. The release profiles of model drugs benzocaine, caffeine, lidocaine and diphenhydramine (DPH) in the polymer films were studied. Basic film forming polymers employing hydroxyl propyl methyl cellulose (HPMC), methylcellulose (MC), and poly ethylene oxide (PEO) were benchmarked with commercial films.[68] **Ming et al. (2006)** prepared and evaluated the films prepared by using different film-forming polymers. Developmental work has been reported for fast-dissolve oral films that employ various water-soluble polymers and achieve rapid disintegration, good mouth feel, and mechanical properties. The water-soluble polymers used for this study were methocel (HPMC) E3, K3, A3, A5, A6 and A15; and polyox N10, N80, N750 and 205. Other water-soluble polymers investigated include pullulan, carboxy methyl cellulose, hydroxyl propyl cellulose, polyvinyl pyrrolidone, sodium alginate, pectin, and gelatin. The desirable fast disintegration and mechanical properties can be tailored with polyox and HPMC.[69] **Fulzele et al. (2002)** explained that polymerized rosin (PR) a novel film forming polymer is characterized and investigated in the present study for its application in drug delivery. Films were produced by a casting/solvent evaporation method from plasticizer free and plasticizer containing solutions. Films prepared from different formulations were studied for their mechanical (tensile strength, percent elongation and Young's modulus), water vapour transmission and moisture absorption characteristics. Neat PR films were slightly brittle and posed the problem of breaking during handling. Hydrophobic plasticizers, dibutyl sebacate and tributyl citrate, improved the mechanical properties of free films with both the plasticizers showing significant effects on film elongation. Release of diclofenac sodium (model drug) from coated pellets was sustained with high coating levels. Concentration of plasticizer was found to affect the release profile. PR films plasticized with hydrophobic plasticizers could therefore be used in coating processes for the design of oral sustained delivery dosage forms.[70]

CONCLUSION

Drug release may be either quick or slow by varying the rate of dissolution of the films. The breath freshening strip was created by Pfizer's Warner-Lambert's consumer healthcare division, which launched Listerine Pocket Paks™ in 2001. Chloraseptic relief strips were the first oral thin film product to incorporate a drug and were introduced in the United States in September, 2003 by Prestige Brands international for relief of sore throat. Zengen Inc developed this new delivery technology, which is a medicated oral strip structured as a proprietary bilayer system. These films typically contain water soluble hydrocolloids such as HPMC, pullulan, pectin, carboxymethyl cellulose, an effective dose of active agent, other additives such as flavoring agents, plasticizers and preservatives. The disintegration and dissolution characteristic of thin film is dependent on thickness and combination of hydrocolloids. MDFs are inherently water soluble and disintegrate in the oral cavity. They can have muco-adhesion properties that cause the dose to adhere to any mucosal surface within the oral cavity until disintegration is complete. Upon complete disintegration, absorption of the API may occur through the buccal mucosa. Esophageal absorption may also occur during the process of swallowing saliva that contains the dissolved API. The majority of the dose ultimately ends up in the stomach and is absorbed in the GI tract in a similar manner as a traditional tablet. A traditional oral dosage form requires a fixed amount of time for stomach fluids to dissolve the entire tablet or capsule.

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