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MOUTH DISSOLVING FILMS: A REVIEW

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ABSTRACT

Mouth dissolving film is the most advanced oral solid dosage form due to its flexibility and comfort in use. Mouth dissolving films are oral solid dosage form that disintegrate and dissolve within a minute when placed in mouth without taking water or chewing. Many Pharmaceutical companies and academic experts across the world are already in the process of exploring the true potential of these films in delivering drugs not only from synthetic source but also from natural source. The beauty of this unique drug delivery system is that they don't need water for consumption, as we see with consumption of conventional dosage forms (tablets, capsules), by the subjects. In addition, these delivery systems are excellent in gaining patient compliance in general and particularly the pediatric and geriatric patient population. This dosage form allows the medication to bypass the first pass metabolism so bioavailability of medication may be improved. Mouth dissolving film has potential to improve onset of action lower the dosing and eliminate the fear of chocking. Formulation of mouth dissolving films involves both the visual and performance characteristics as plasticized hydrocolloids, API taste masking agents are being laminated by solvent casting and semisolid casting method. Solvent casting method being the most preferred method over other methods because it offers great uniformity of thickness and films prepared having fine glossy look and better physical properties. Mouth dissolving films are evaluated for its various parameters like thickness, physical property like folding endurance, disintegration and dissolution time. This review gives an idea about formulation techniques, evaluation parameters, overview on packaging and some available marketed products of mouth dissolving films.

INTRODUCTION

The oral route of administration have always been preferred over the other routes of administration namely, parenterals, topical, rectal and vaginal by the medical practitioners, manufacturers due to patient acceptance. Ease of administration, convenience and cost effectiveness has been the reason behind the popularity of this route among the patient population. The oral cavity has unique environment that offers its potential as a site for drug delivery. There has been a lot of advancement in the oral solid drug delivery system, from conventional dosage forms such as tablets and capsules to modified release dosage forms and recently the mouth dissolving dosage forms (Fig. 1). The limitation of difficulty in swallowing oral solid dosage forms has been the reason for the evolution of mouth dissolving drug delivery system.

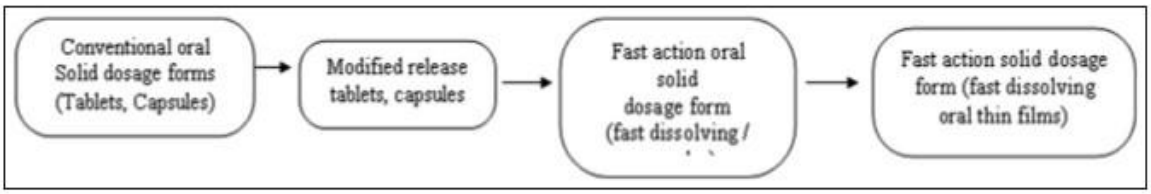

Figure 1: Stages in the Development of Oral Dosage Forms.

Mouth Dissolving films are oral solid dosage forms that disintegrate and dissolve when placed in the mouth without taking water. Mouth dissolving films are gaining popularity and acceptance among the pediatric, geriatric and dysphagia patients who fear choking. Mouth dissolving films provides convenience, ease of administration and faster onset of action, as the drug is absorbed through oral mucosa and enters the systemic circulation, bypassing the first pass metabolism.[1] Mouth dissolving film is a novel approach of the oral drug delivery, which is based on platform technology of the transdermal films and patches. The delivery approach contains a very thin film containing mainly polymer and plasticizer, which is designed to put on the tongue or anywhere in oral cavity. These films quickly become wet by salivary fluid and they are hydrated and disintegrated inside oral cavity in fraction of a minute. Then they dissolve quickly and release the active agent for oral absorption. While comparing with other mouth dissolving drug delivery system like orodispersible tablets, the mouth dissolving films are produced by continuous process on production scale equipments with comparative low production cost.[2]

DRAWBACK OF CONVENTIONAL DOSAGE FORMS[3]

1. Difficulty in swallowing [dysphasia] or chewing in some patients particularly pediatric and geriatric patients.
2. Water is required to swallow
3. More susceptible to degradation via humidity and temperature.
4. Most of Patient incompliance.
5. Occurs Bioavailability problem
6. Drug action will be seen after long time as compare to MDFs.
7. Liquid oral dosage form having a Stability problem

Advantages of Mouth Dissolving Films[4]

1. Large surface area: Film has thin, elegant and comparative larger surface area. So, it disintegrates and dissolves rapidly in oral cavity.
2. Superior to orodispersible tablets: Orodispersible tablets are very fragile due to low hardness of tablets. Therefore, special packaging system is required to protect tablets during transportation and storage. The films are not fragile like the orodispersible tablets. So, it is too easy to carry films compared to fragile ODTs during patient handling.
3. Superior to liquid dosage forms: In case of oral liquids such as solution, syrups and suspensions, dose precision is not achieved due to manual handling of patients. Films are unit dose formulation like tablets and capsules. The Dosage form combines advantages of solid and liquid dosage form. Enhanced stability compared to liquid formulation and enhanced disintegration compared to solid dosage forms.
4. No need of water: Patients have no swallowing problem because films are dispersed in oral cavity. Films are dissolved in saliva. So, water is not required for intake of dosage form. Mouth dissolving film overcomes the problems found during swallowing of tablets and capsules. The film has larger surface area compared to other dosage forms. Therefore, it quickly comes in contact with saliva. Consumers can take this dosage form at any place, any time without need of water as per their convenience.

Disadvantages of Mouth Dissolving Films[5]

1. High dose of the drug cannot be incorporated into the film
2. Taste masking is essential if the drug is having a bitter taste
3. Packaging needs special care and equipments

4. The technical challenges in manufacture of films include achieving dose uniformity and uniformity in thickness of mouth dissolving film while casting of the film

STRUCTURE AND SECRETIONS OF ORAL CAVITY[6-8]

Epithelial Layer

Oral epithelium is to provide a protective surface layer between the oral environment and the deeper tissues. The oral epithelium has a squamous epithelium of tightly packed cells that form distinct layers by a process of maturation from the deeper layers to the surface. The pattern of maturation differs in different regions of the oral mucosa due to the variation in the specific function of the tissues. The surface layer of the hard palate and tongue forms keratin to yield a tough, non-flexible epithelial surface resistant to abrasion, but the epithelium of the cheek, floor of the mouth, and soft palate is non keratinized and facilitates distensibility.[6]

Table 1: Epithelial thickness of different oral cavity regions.

S.No	Oral cavity regions	Thickness (µm)
1	Hard palate	100–120
2	Buccal mucosa	500–600
3	Lip mucosa	500–600
4	Floor of the mouth	100–200

Vascular System of Oral Cavity

The blood supply to the oral cavity is delivered predominantly through the external carotid artery. The maxillary artery supplies the main cheek, hard palate, and the maxillary and mandibular gingiva. The internal jugular vein eventually receives almost all of the blood derived from the mouth and Pharynx.[7]

Salivary Secretions of Oral Cavity

The primary protection of oral cavity is offered by epithelial layer and in order to maintain a moist surface three pairs of salivary gland secretes ‘saliva’. Salivary secretion is supplied by three pairs of glands, namely,

1. Parotid (under and in front of the ear)
2. Submaxillary (below the jaw)
3. Sublingual (under the tongue)

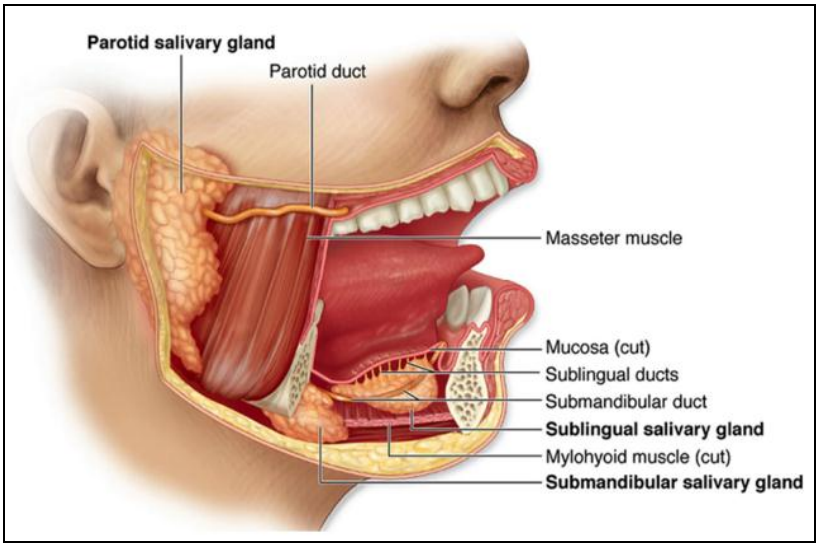

Figure 2: Salivary glands of human oral cavity.

Blood supply to the salivary glands and their ducts by branches of the external carotid artery and afterwards, travelling through the many branch arteries and capillaries, returns to the systemic circulation via the jugular veins.[8]

Saliva

Saliva is viscous, colourless and opalescent, hypotonic compared to plasma (between 110 and 220 milli Osmoles per litre), with a specific gravity of about 1.003. The pH varies 7.4 to 6.2 (low to high rates of flow), but the action of bacteria on sugar can reduce the pH to between 3 and 4 around the teeth. Saliva is mainly composed of water, mucus, proteins, mineral salts, and amylase.[8]

CLASSIFICATION[9-14]

Mouth Dissolving Films are mainly categorized in two parts, mucoadhesive films and flash release wafers

1. Mucoadhesive films

The Mucoadhesive film is applied to buccal and gingival mucosa and sticks to mucosal surface. Carbomers 974P and 971P are most widely used polymers for bioadhesion purpose. Mucoadhesive films are generally prepared by hot melt extrusion as well as solvent casting. As per the function and disintegration time, mucoadhesive films are categorized in two parts.[9]

(i) Mucoadhesive melt away strip: It sticks to the mucosa; totally dissolves within fraction of a minute and continuously releases the drug over time. Melt away films are generally prepared as monolayer films.

(ii) Mucoadhesive extended release film: This type of oral wafer sticks to mucosal surface and remains there for up to several hours. For that duration, drug release is sustained and wafer must be removed at the termination of medication. Oramoist is an extended release oral mucoadhesive film that sticks to the upper surface of oral cavity and enhances salivary secretion to prevent dry mouth syndrome (xerostomia). Sustained release films are prepared as monolayer as well as multilayer multiparticulate containing films.[10,11]

2. Flash release films or wafers

Flash release wafers dissolve in maximum of 60 s and immediately release the drug in oral cavity. As per the site of application, the flash release wafers are categorized in two parts.[12]

(i) Orodispersible film (ODF): The ODF is very thin strip with actives and water soluble excipients, mainly film forming polymers and plasticizers

(ii) Sublingual films: Formulation of sublingual film is similar to ODFs but the films are placed under a tongue rather than in oral cavity. Reckitt Benckiser pharma formulated Suboxone-buprenorphine and naloxone sublingual films which are used for maintenance treatment of opoid dependence.[13]

Table 2: Comparison of Different Types of Oral Films and Their Major Characteristics.[14]

Properties	Orodispersible films	Sublingual Film	Bucoadhesive Melt away film	Bucoadhesive extended release wafer
Area (cm2)	Generally between 2 cm2 to 8 cm2	Generally between 2 cm2 to 8 cm2	Generally between 2 cm2 to 7 cm2	Less than 4 cm2, most preferably between 2 cm2 to 4 cm2
Thickness (µm)	< 70 µm	< 70 µm	< 500 µm	<250 µm
Number of layers	Monolayer	Monolayer	Mono or multilayer	Multilayer system
Property of excipient	Water soluble low mol. wt., low viscosity grade polymers	Water soluble low mol. wt., low viscosity grade polymers	Water soluble high mol. wt., high viscosity grade polymers	Hydrophilic or hydrophobic, high mol. wt., high viscosity sustained release grade
Drug loading form	Suspended or solubilized form	Suspended or solubilized form	Suspended or solubilized form	Suspended or solubilized form
Properties	Orodispersible films	Sublingual Film	Bucoadhesive Melt away film	Bucoadhesive extended release wafer
Route of	Oral cavity	Under tongue	Buccal mucosal	Buccal, gingival or any

application			surface	oral mucosa
Disintegration	Maximum within 1 min	Maximum within 1 min	Within few minutes and forms viscous gel	Sticks up to max. 12 h and sustains drug release

Ideal Characteristics of A Suitable Drug Candidate[15]

1. It shall have high solubility and permeability (BCS – Class I drug)
2. The drug should have pleasant taste.
3. The drug to be incorporated should have low dose up to 40 mg.
4. The drug should have smaller and moderate molecular weight.
5. The drug should have good stability and solubility in water as well as saliva.
6. It should be partially unionized at the pH of oral cavity.
7. It should have ability to permeate the oral mucosal tissue.

Ideal Composition of Mouth Dissolving Film[16]

Table 3: Typical composition of a mouth dissolving film.

Ingredient	Amount	Uses (Example)
Drug	5-30 %w/w	All drug with low dose
Water soluble polymer	45% w/w	Film forming capability (HPMC E3, E5, E6, E15, K3, Methyl cellulose A3, A6, A15, Pullulan, Polyvinyl pyrollidon K-90, Pectin, gelatin, Sodium alginate, Hydroxy propyl cellulose, Polyvinylalcohol, Maltodextrin)
Plastisizers	0-20 %w/w	Increases the flexibility and reduces the brittleness of film (Glycerol, Polyethylene gycol, Dibutylpthallate,triethyl citrate)
Surfactant	q.s.	Used as solubilizing and wetting agents (Tween 80,Sodium lauryl sulphate)
Sweetning agent	3-6 %w/w	Increasing the palatability of the film (Aspartame, Saccharin,Cyclamate,Alitame and Neotame, Acesulfame-K)
Saliva Stimulating agent	2-6 %w/w	Increases the saliva stimulation for faster dissolution of film (Citric acid, Malic acid)
Colors, Flavors	Up to 1% w/w	Silicon dioxide (pigment) is used as coloring agents. Fruity flavors like cocoa, apple, raspberry are widely used.

Formulation Consideration For Mouth Dissolving Film

Formulation of mouth dissolving film involves the careful selection of excipients to impart aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, and mouth-feel etc. From the regulatory perspectives, all excipients used in the formulation of mouth dissolving film should be Generally Regarded as Safe [i.e. GRAS-listed] and should be approved for use in oral pharmaceutical dosage forms.[17]

1. Active Pharmaceutical Ingredients

The active pharmaceutical ingredient used in the formulation can belong to any class but should fulfill the requirements. Some of the examples of various classes of drugs that can be incorporated into MDFs include anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, antiemetic, etc. Common examples of drugs incorporated into MDFs are salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin.[18]

2. Water soluble polymer

A variety of water soluble polymers can be used in the preparation of mouth dissolving films. The polymers can be used alone or in combination to achieve the desired film properties.[8] There are several characteristic properties of the oral film can be controlled with type or grade of polymer include mucoadhesiveness, disintegration time, drug loading capacity, mechanical strength, elasticity, handling properties.[19]

The choice of the polymer should be made based on the following criteria.

1. The polymer should be non toxic and non irritating.
2. It should be inert and tasteless.
3. It should not have impurities which could leach into the product.
4. It should readily disintegrate.
5. It should have good wettability and spreadability.
6. The polymer should form a film has good shear and tensile strength so that it can be manufactured on a large scale on machines.

Some examples of the water soluble polymers used as film former include various grades of HPMC, methyl cellulose, pullulan, carboxymethyl cellulose, polymerized resinpolyvinylpyrollidone PVP K-90, pectin, gelatin, sodium alginate, hyroxypropylcellulose, polyvinyl alcohol, maltodextrins and eudragit RD10.[19]

3. Plasticizer

The plasticizer is an vital ingredient that helps to improve the film flexibility and reduce brittleness. Use of inappropriate plasticizer may result in film cracking, splitting and peeling. The plasticizer is added to the formulation in 0-20% concentration range to modify the mechanical properties of the film such tensile strength and percent elongation. Some

examples of plasticizer include PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate.[20]

4. Surfactants

Surfactants are added to solubilise the poorly soluble drug and also to solubilise or wet and disperse the film and release the active ingredients easily. Examples include poloxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzethonium chloride, tweens and spans.[20]

5. Sweetening agent

The mouth dissolving films need to have good taste for patient acceptance and compliance as the films are to be taken without water and they are not swallowed but are required to disintegrate and dissolve in the oral cavity.[21]

6. Saliva Stimulating agents

These agents are added to stimulate saliva production in oral cavity which promotes faster disintegration of mouth dissolving films. Examples include citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid. Citric acid is one of the most preferred ingredients.[21]

7. Flavoring agents

These are added for patient acceptance and compliance. The selection of flavors depends on the age of the patients, type of drug and the taste of drug to be masked. Flavoring agents can be selected from the synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers.[22]

8. Coloring agents

Colors approved by FD &C are used for improving the appearance of film incase the drug is insoluble or for aesthetic appeal. Pigments like titanium dioxide can be used for coloring. The concentration of coloring agent should not exceed 1% w/w.[22]

Formulation of Mouth Dissolving Films

Solvent casting and hot melt extrusion [HME] are main methods for preparation of MDFs. Apart from two methods, semisolid casting, solid dispersion extrusion and rolling method are least useful methods. These methods are adopted alone or in combination as per the required characteristics of final film.[25]

1. Solvent casting method

In solvent casting method, hydrophilic polymers are solubilized in water. The drug and other excipients are dissolved in water or other suitable solvent. Mixing and stirring of both the solutions are done. Then the resultant mixture is cast on the glass petri-pLate or suitable release liners, and dried in hot air oven or other suitable drying assembly.

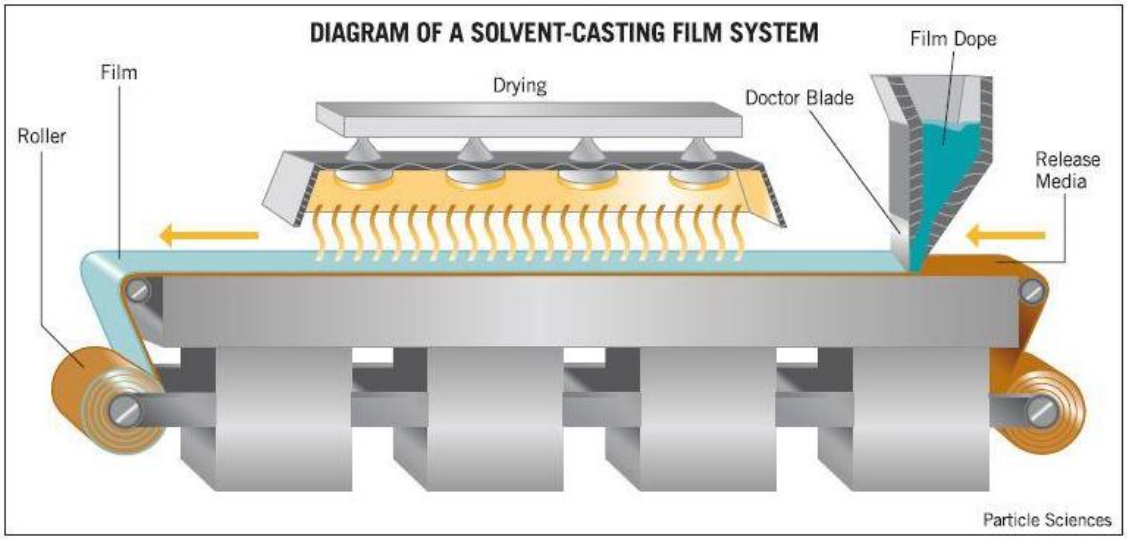

Figure 2: Diagram of Solvent Casting Process.

The selection of polymer is very critical and important factor for the successful development of the mouth dissolving film. The single polymer or multiple polymers can be used as per the desired QTPP and CQA of the final film formulation. The mechanical property of the film is directly linked to characteristics, amount and type of polymer used. The polymer selection should be done by considering consistent mechanical property of prepared final film throughout handling, storage and transportation. Mouth dissolving film dosage form should disintegrate in fraction of a minute when put in mouth. Prepared film should deliver the drug instantaneously after disintegration and dispersion in oral cavity. Film forming polymer is a platform for formulation of mouth dissolving film. It is important and critical component of the mouth dissolving film. Generally 40–45 %w/w film forming polymer should be added considering the total weight of film. Increment or decrement of the polymer concentration is done as per requirement of the film.

Ideal characteristics of film forming polymers are as they should be

1. It should be free from toxicity and irritability
2. It should not contain any impurities

3. Disintegrate rapidly in saliva or should not retard disintegration by forming gel
4. It should be free from bitter and unpleasant taste
5. It should be easily spreadable.
6. It should have good wetting efficiency[26]

2. Hot melt extrusion

Introduction[27]

Though solvent casting is widely accepted method for formulation scientists to cast orodispersible film, hot melt extrusion [HME] has immense potential for the same. Solvent casting has been proved as a benchmark technology because of ease in product development, process optimization, process validation and technology transfer to production scale despite of some drawbacks like consumption of large quantity of solvents with controlled limits of organic volatile impurities in final formulation. The application of HME in the pharma-industry is consecutively increasing due to its proven innumerable advantages like solvent free continuous process with fewer unit operations and better content uniformity. Very few development activities have been initiated in the field of hot melt extruded orodispersible films so far. In HME, active pharmaceutical ingredient is generally blended with polymer, plasticizer and other excipients in solid state. Semisolid blend is passed from extruder. Heater inside the extruder melts the mixture. Molten mass passes from dies and after cooling, molten mass is shaped according to product requirement.

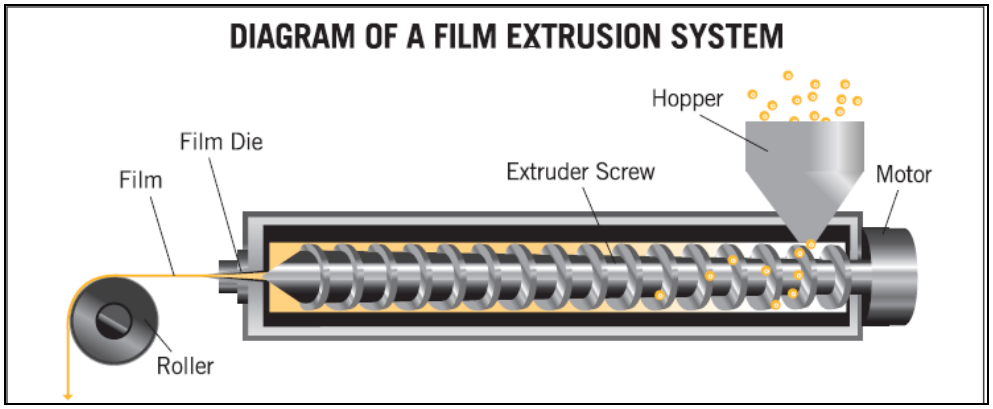

Figure 3: Diagram of Hot Melt Extrusion Process.

Types of extruders[28]

Pharmaceutically adopted extruders are used to mix active pharmaceutical ingredient with polymer, plasticizer and excipient blend. In this section, different part of extruders has been discussed with special emphasis on ODF formulation.

a] Ram extruder: Ram extruder contains piston like assembly which pushes molten mass in heating chamber of extruder. Ram extruder is generally not preferred in ODF preparation by HME due to its low temperature uniformity and improper mixing abilities

b] Screw extruder: Screw extruders are most widely accepted for pharmaceutical industry. Screw extruder contains a pre-heated barrel in which screw rotates. The ram extruders are generally used for simple mixing while the screw extruders are used for high shear mixing. In pharmaceutical industry, two types of screw extruders are widely used as per requirement of product.

[A] Single-screw extruder: In this type of extruder, a single screw rotates to feed, melt, de-volatilize and pump the molten mass inside the pre-heated barrel, intense mixing cannot be achieved with single screw extruder.

[B] Twin-screw extruder: Twin-screw extruder consists two rotating screw inside the pre-heated barrel. This extruder has higher kneading and intense mixing capacity compared to singlescrew extruder. Issues such as over-heating and shorter transit times are generally less found with this extruder. Twin-screw extruders are further classified as per their installation and working mechanism of screw. One is co rotating and another is counter-rotating design. In co-rotating extruder designs, screw rotates in same direction and they can be rotated at high speed and gives more output than counter-rotating extruders. In counter-rotating extruders, two screws rotate in opposite directions. The counter-rotating extruders are generally preferred when high shear mixing is required. Potential air entrapment is found with counter-rotating extruders. So, they are not preferred for products sensitive to oxidative degradation. Also rotating speed of screws is slow. So, rate of output is very less. Basic structural difference of different variants of screw extruders is shown in Fig 4.

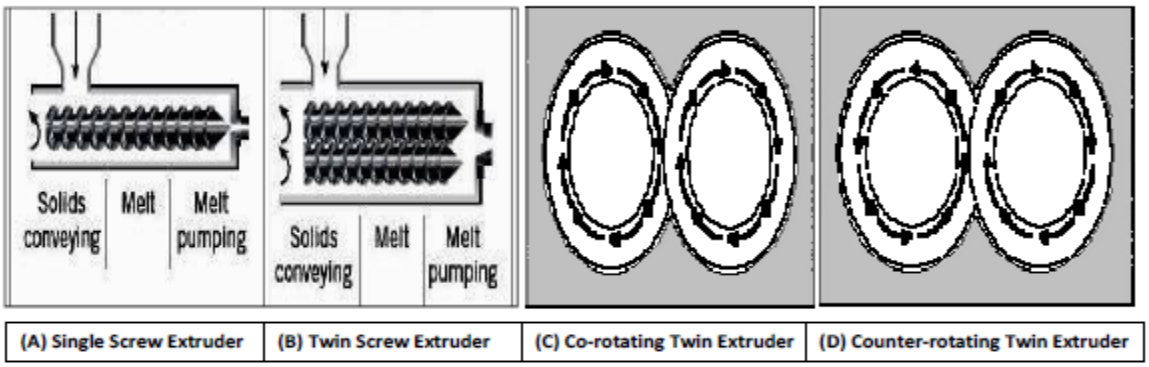

Figure 4: Schematic diagram of different variants of screw extruders.

TASTE MASKING TECHNOLOGIES

Taste masking is defined as reduction of perception in mouth to an undesirable obnoxious taste that would naturally present.[29]

1) Taste Masking with Flavors, Sweeteners and Amino Acids

Natural and synthetic flavors are used to mask the bitter taste of formulation. Peppermint, lemon, orange, mixed fruit and chocolate are widely used flavors in taste masking. Phosphorylated amino acids are also used as flavoring agents. E.g. phosphor-tyrosine.[30]

2) Taste Masking With Lipophilic Vehicles

- Lipids: Oils, lipids and fatty acids enhance viscosity of dosage form in mouth. They make lipophilic layer on taste bud. So, they work as taste-masking agents. E.g. carnauba wax, glyceryl monostearate, hydrogenated soybean oil, stearyl stearate.
- Lecithin and Lecithin-like Substances: Soyalecithin is a bitter-taste suppressant. Soyabean derived phosphatidic acid and milk derived β-lactoglobulin are widely used to mask the taste of caffeine, quinine and papaverine hydrochloride.
- Liposomes: Liposomes are a vesicular structure in which bitter and obnoxious actives are entrapped. Liposomes prevent contact of bitter active from saliva and taste buds. So, perception of bitterness cannot be experienced.[30]

3) Coating of drugs using a suitable polymer

In this approach, bitter active substance is coated with suitable coating material which makes a barrier layer around drug particle. Coating material should be selected on such a way that it may not affect release profile of active substance.

- Cellulosic coating materials: Hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose and methyl cellulose.
- Enteric polymers: Eudragit, shellac and other phthalate derivatives are widely used to mask bitter taste.
- Proteins, peptide and zein: Protein and peptide can make a barrier layer around bitter drug particle. Gelatin and its hydrolyzed form are also used to mask some bitter tasting drugs. Prolamines such as zein and gliadin are proteinous molecules obtained from cereals. They are also used to improve mouth-feel of bitter tasting drugs.[29]

4) Inclusion Complexation

In inclusion complex, the active substance is entrapped in to the internal cavity of host molecules. By inclusion complex formation, the host molecules decrease the exposure of the drug in oral cavity and tongue. Sometimes it decreases solubility of drug in salivary fluid. So, taste masking occurs. B-Cyclodextrin is preferred inclusion-complex forming agent for taste masking purpose.[30]

5) Use of Ion-exchange Resin

Ion-exchange resins are resin molecules which have high molecular weight. They are either cationic, anionic and zwitter ionic in nature. Styrene and divinyl benzene are widely used resins for exchanging the cationic or anionic molecules. Ion-exchange resin forms complex with oppositely charged drug molecule and makes complex which cannot dissociate in saliva. When drug-resin complex comes in the contact with 0.1N hydrochloric acid of stomach, weak ionic bonds of drug-resin complex dissociates and drug molecule is absorbed from mucosa. Ion-exchange resins are classified as per their acidity and alkalinity. Cationic-exchange resins may be strong acidic or weak acidic in nature while anionicexchange resins are strong basic or weak basic in nature.[31]

6) Solid dispersion

Solid dispersion is a solid state dispersion formation of drug into matrixing agent. Melt-dispersion method, solvent-dispersion, meltevaporation method, hot-melt extrusion process, lyophilization technique, melt-agglomeration method, SCF-Supercritical fluid technology, dropping solution method and co-precipitation method are some of the widely accepted method for solid dispersion preparation.[29,30]

7) Microencapsulation method

In this method, solid particles, liquid droplet or semisolid material is coated with thin polymeric layer. Generally coating polymers used in this method are insoluble at salivary pH and polymeric coat ruptures after reaching to the stomach.[31]

8) Prodrug approach

Prodrugs are chemically modified inactive molecule which is metabolized to active drug moiety. Esterification of drug molecule is widely used approach for prodrug synthesis. E.g. palmitate esters of clindamycin and choramphenicol improve taste of parent drug molecule.[29]

9) Multiple emulsion

Multiple emulsion is formulated by incorporating active pharmaceutical ingredients in internal aqueous part of w/o/w type emulsion or in internal oil part of o/w/o type emulsion. So, bitter drug cannot come into contact with taste receptors of the mouth.[29]

10) Spray drying

In this technique, bitter tasting drug is dissolved or dispersed in hydrophilic polymer solution. This polymeric solution is atomized in spray dryer. Thus microparticles of drug and polymer are formed. Generally, hypromellose and povidone are used as hydrophilic polymers.[31]

11) Adsorbates

Bentonite, vegum and silica gel are widely accepted adsorbates for taste-masking. The active molecule is adsorbed on porous structure of adsorbate. So, drug desorption from adsorbate surface is delayed inside The oral cavity. So, direct exposure of active to saliva is delayed.[29]

12) pH Modifiers

pH modifiers change microenvironment of bitter active drug. Due to change in micro-environmental pH, solubility of bitter active decreases in saliva. So, taste perception is inhibited.[29]

13) Anesthetizing agent

Anesthetizing agents inhibits nerve terminals of taste receptors of tongue. So, taste sensation cannot be experienced by tongue.[29]

14) Viscosity enhancers

Viscosity enhancers decrease diffusion of bitter active substance from formulation to surrounding saliva. So, very minute amount of drug can reach to taste receptors. Xanthan gum, Hypromellose, sodium carboxymethylcellulose are widely used viscosity imparting agents.[31]

Packaging of Mouth Dissolving Film

There are many packaging options available for mouth dissolving films. Single packaging is mandatory for films. An aluminum pouch is the most commonly used packaging material. The ideal properties of material selected for packaging include:

1. They must protect the preparation from environmental conditions.
2. They must be approved by FDA.

3. They must meet applicable tamper resistant requirements.
4. They must be non-toxic.
5. They must be inert and not react with the product.
6. They must not impart taste or odor to the product.[32]

The mouth dissolving films can be packed using single pouches, blister card with multiple units, multiple unit dispenser, and continuous roll dispenser. A vertical or horizontal form fill seal equipment is used to form flexible pouch. Single or aluminum pouches are preferred. The pouch may be transparent for product display. Usually one side of the pouch is transparent and other side has foil lamination. There is zero transmission of gas and moisture with foil lamination. Aluminum pouch is the most commonly used pouch. The blister card 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.[33]

CQAs OF MOUTH DISSOLVING FILMS

1. Physical strength

Appropriate physical strength, is one of the most evident CQA of the oral films. The product should have suitable mechanical properties so it can be easily manufactured, packaged and handled without damage or break. However, there are no guidelines with the description of the most adequate properties, methods and ranges that should be studied. However, in literature there is a general consensus about the main properties that should be tested: elongation at break, young's modulus and tensile strength. The literature review highlighted the difficulty of stablishing strict ranges for these parameters and a wide variation may be appropriate depending on the polymeric matrix under development. In fact, the appropriate value for the mechanical strength may vary significantly depending on the polymeric matrix and method of manufacture An appropriate balance should be found between these properties.[34]

2. Physical Appearance

The physical appearance of the film is important. Selection of suitable size and shape is important depending on the site of application. The amount of dose to be incorporated also influences the size of the film. The mouth dissolving films are cut into strips of suitable size and are weighed in triplicate on electronic balance. The thickness of the film is checked at three different locations i.e. corners and at the centre. The average and standard deviation of three films is determined.[35]

3. Organoleptic Characteristics

One limitation in all orally administered dosage form is their odor and taste should be acceptable to the patients. This is a characteristic which depends on the properties of drug like bitterness, particle size, solubility, ionization. The mouth dissolving film should have agreeable taste, after taste and mouth feel. The appropriate choice of flavor is affected by the taste conferred by drug and the flavor or combination of flavors required to mask the taste giving a good balance of acid or sour or salty taste and covering any unpleasant aftertaste.[36]

4. Mechanical Properties

The mouth dissolving films should have suitable mechanical properties so that it can be easily manufactured, packaged and handled without damage or break. The mechanical properties test includes tensile strength, percent elongation and folding endurance. There is no guideline till date which gives any specifications or range in which the test values should belong. The formulator has to seek an appropriate balance in these properties.[37]

5. Dose Uniformity and Drug Release

The control on weight and thickness of the film is important for obtaining dose uniformity. The target drug release profile should be defined in early stages of the development of the product based on the target product profile. Disintegration time and dissolution profile of the mouth dissolving film are important test for evaluation of release of drug.[37]

6. Residual Water Content

The residual water content is an important parameter which should be considered as it affects the properties of the film significantly. The mechanical properties of the film are affected depending on the water content in the film. In case of loss of water molecules from polymer matrix it can result in brittle film while presence of excess water or absorption of water molecules from atmosphere on exposure to environment may result in sticky films. Hence control over environment conditions i.e. temperature and humidity during manufacture and packaging of mouth dissolving films is essential.[38]

7. Stability

The physical and chemical stability of the drug in its final pharmaceutical dosage form is essential. Various screening test and stability test can be done to confirm the stability of the dosage form in the final package using the controlled temperature and humidity conditions as per ICH stability guideline.[38]

COMMERCIALLY AVAILABLE MOUTH DISSOLVING FILMS

Table 4: Marketed formulations.[39-50]

Sr.No	Brand	API	Category/Use	Manufacturer /marketed
1	Labtec GmbH Ondansetron Rapid film®	Ondansetron	Anti emetic	Monosol Rx, Bioalliance Pharma SA
2	Zuplenz®	Ondansetron	Anti emetic	Strativa Pharmaceuticals, Par Pharmaceutical Company
3	Setofilm	Ondansetron	Anti emetic	Norgine Pharmaceuticals Ltd
4	Donepezil Rapid film®	Donepezil Hydrochloride	Anti Alzheimer	APR applied Pharma research & Labtec GmbH
5	Olanzapine rapid film	Olanzapine	Schizophrenia and bipolar disorder	APR applied Pharma research & Labtec GmbH
6	LISTERINE POCKETPAKS	Cool Mint	Mouth freshener	Johnson & Johnson
7	Benadryl allergy Quick Dissolve	Diphenhydramine HCL	Anti allergic	Pfizer/McNeil Consumer Healthcare division
8	Triaminic	Diphenhydra mine HCL	Anti allergic	Novartis
9	Chloraseptic® Relief Strips and Chloraseptic® Kids Sore Throat Relief Strips	Benzocaine and Menthol	Sore throat	Prestige
10	Suppress™ Cough strips with Dextromethorphan	Dextromethorphan hydrobromide	Cough, Bronchial irritation	Innozen Inc
11	Theraflu	Dextromethorphan HBR	Cough Suppressants	Novartis
12	Gas X	Simethicone	Anti Flatulance	Novartis
13	Sudafed PE	Phenylephrine	Relieving Congestion	Wolters Kluwer Health Inc
14	Zolmitriptan Rapidfilm	Zolmitriptan	Antimigrane	APR Applied Pharma Research, Labtec Pharma
15	KP106	D-amphetamine	Attention Deficit Hyperactivity Disorder	MonoSol Rx and KemPharm
16	Pedia-LaxTM Quick Dissolve Strip	Sennosides	Constipation and Bowel Cleanser.	C.B. Fleet
17	SEDERA	Sildenafil citrate	Erectile dysfunction.	CL Pharm Co. Ltd and KWANG DONG
18	Smart Film	Sildenafil citrate	Erectile dysfunction	Pfizer Inc

19	Suboxone	Buprenorphine and Naloxone.	Opioid dependency	Reckitt Benckiser Pharmaceutical Inc
20	Onsolis™	Fentanyl	Breakthrough Pain in Patients with cancer	Biodelivery Sciences & Meda AB
21	BEMA™	Buprenorphine	Opiod analgesic	Biodelivery Sciences
22	Methylcobalam in Oral disintegrating strips	Methylcobalamin	Peripheral neuropathy, Diabetic neuropathy	Shilpa Therapeutics
23	Rapid dissolving film	Amlodipine besylate	Hypertension, Angina	Kyukyu Pharmaceutical Co Ltd.
24	Penerect 50	Sildenafil	Erectile dysfunction	Shilpa Therapeutics
25	TFL-10/20	Tadafil	Erectile dysfunction	Shilpa Therapeutics
26	Up-n-Up	Caffeine+ Multivitamin	Dietary supplement	Aavishkar Innovations for healthier life
27	D-Fence	Vitamin D3	Build Immune system	Aavishkar Innovations for healthier life
28	Melatonin : sleep strips	Melatonin, L-Theanine	Induces Sleep	Aavishkar Innovations for healthier life
29	Clonazepam Orally disintegrating strips	Clonazepam	Acute Seizures	Zim Laboratories
30	CUREfilm@ β-Caryophyllene	B- Caryophyllene	Anti inflammatory, Analgesic	Cure Pharmaceutical

CONCLUSION

The flexibility of this dissolvable film technology platform offers future potential for expanded applications across different delivery routes in multiple pharmaceutical, biopharmaceutical, and medical markets. It also provides an opportunity to extend revenue life cycles for existing drugs whose patent is expiring and will soon be vulnerable to generic competition. In other words, oral films allow the lifecycle management of the products. Additionally, the majority of the manufacturing approaches used are well understood and easily controlled, prompting a robust and efficient development from bench to market. While mouth dissolving films appear to be simple but they do pose extreme challenges in manufacturing and attaining an mouth dissolving film that can gain acceptance by the end-user, key acceptability attributes like stickiness and disintegration time. The future market potential for them is thick and bright. There are some important issues that should be taken in consideration regarding the oral films development, manufacturing and marketing. During the development the critical quality attributes should be well-stablished to prevent unfortunate and uncontrolled events. Despite the complexity of the formulation and process, a deep knowledge of the system may be sufficient to control and surpass some inevitable and

unpredictable proceedings. Finally, it is important that the combination of thin film technology with the selected drug substance gain wide consumer acceptance and pave the way for other medicines to move to this portable, exceptionally convenient pharmaceutical form. There is no ambiguity that they are going to be the most attractive dosage forms across all age groups with a full potential to gain patient compliance in all disease conditions.

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