Mouth Dissolving Films for Patient-Centered Drug Delivery: An Innovative Review

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***Abstract*—Mouth-dissolving films (MDFs) represent a modern and patient-friendly oral drug-delivery system designed to rapidly disintegrate in the oral cavity without the need for water. They offer significant advantages for paediatric, geriatric, and dysphagic patients while improving onset of action, bioavailability, and therapeutic compliance. This review provides a comprehensive overview of MDFs, including their mechanisms of action, classifications, and essential formulation components such as polymers, plasticizers, sweeteners, and active pharmaceutical ingredients. Various preparation methods—such as solvent casting, hot-melt extrusion, semisolid casting, solid dispersion, and rolling techniques—are discussed along with critical evaluation parameters like mechanical properties, disintegration time, dissolution behaviour, drug content, and stability. Although MDFs face formulation challenges such as limited drug-loading capacity, moisture sensitivity, and taste-masking requirements, they remain a promising platform for efficient and convenient drug delivery. This review highlights recent advancements, formulation strategies, and quality considerations, demonstrating the growing importance of MDFs in pharmaceutical innovation.**

***Index Terms*—First-pass metabolism, Mouth-dissolving films, Oral drug delivery, Rapid drug release.**

I. INTRODUCTION

Advancement in the field of medicine has provided us with executable substitutes ranging from Oral route for pediatrics, bed rid, gerontological, nauseous patients. Buccal drug delivery has lately become an important route of drug administration. A variety of bio adhesive mucosal dosage forms have come up into picture and are being used extensively. They include glutinous tablets, ointments, conjoins, gels and most recent one being the use of polymeric films for buccal delivery commonly referred as mouth dissolving films. Mouth dissolving films is a fresh drug transfer organism for the oral consumption of the drugs. Transdermal patch technology is used for the development of the same. In this system, slim oral strip of the medicine is placed on patient's tongue or on oral mucosal tissue which is acted upon by saliva. It gets hydrated rapidly and sticks where it is placed. It quickly degenerates and dissolves to release the medicine for oromucosal absorption or will be swallowed and retain its disintegration action during gastrointestinal absorption. These films are more affordable to make compared to the commonly used fast-dissolving methods that use lyophilized products, because their manufacturing process is less expensive and more competitive.[1]

Oral thin films have been identified as a recognized alternative to contemporary OTC medicines such as tablets, liquids and capsules by both, the consumers as well as the pharmaceutical companies. OTFs propose a rapid, precise dosing in an oral thin film offer fast, accurate dosing in a harmless, effectual format that is appropriate and handy with the added advantage of no requirement of water or precise quantity of dosage. They are the size of a postage stamp and degenerates rapidly releasing one or more APIs in seconds when placed on patient's tongue.

The oral route remains the most widely accept ed route of drug administration due to the numerous merits offered over other routes. This route of administration is non-invasive, requires no special training, toxicities and over-dosage can be easily managed. However, what is a major disadvantage, especially in children and elderly patients, is difficulty in swallowing tablets and capsules. Oral dissolving films help solve the problem of people having trouble swallowing or being afraid of choking on tablets, capsules, or dissolving tablets. This is especially helpful for children and elderly people. The films are ultra-thin formulations of postage stamp size and contain active ingredients and

excipients. They are usually administered by the sublingual or buccal routes. Films deliver a measured dose of a drug to the site of administration and thereby offer an advantage over creams and ointments.[2]

II. MECHANISM OF FILM FORMATION [2]

Film forming system is applied directly to the skin and it forms a thin, transparent film in situ upon solvent evaporation as shown in fig. 1. After application of the formulation to the skin, the composition of the film forming system changes significantly due to the loss of the volatile components of the vehicle which results in formation of residual film on the skin surface. In this process the concentration of drug increases, reaching saturation level and with the possibility of reaching super saturation level on the skin surface. Supersaturation results in the enhanced drug flux through the skin by increasing the thermodynamic activity of the formulation without affecting the skin's barrier, thereby reducing the side effects or irritation.
The concept of supersaturation can be explained by the modified form of Fick's law of diffusion. Fick's law of diffusion given by Eq.:

$$J=DKCv/h$$

Where J = rate of drug permeation per unit area of skin per unit time (flux) D = diffusion coefficient of drug Cv= concentration of drug h = thickness of barrier to diffusion

From this equation, it is clear that the rate of drug permeation across the skin is proportional to the concentration of the drug. However, this is true when the entire drug is dissolved in the vehicle. Equation describes the modified form of Fick's law of diffusion:

$$J = \alpha D/\gamma h$$

Where a=thermodynamic activity of drug within formulation γ=thermodynamic activity of drug within membrane

According to this equation, the flux of the drug is directly proportional to the thermodynamic activity of the system, which is related to saturation. However, increasing the super saturation increases thermodynamic instability.

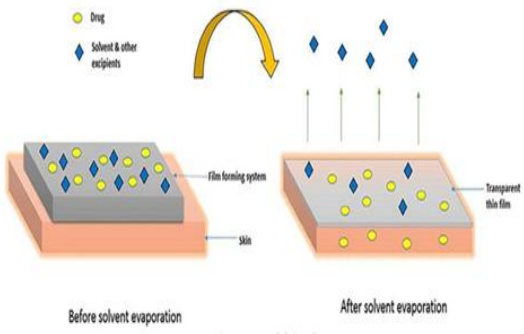

Fig. 1: Mechanism of film formation.

III. TYPES [3]

ODFs are generally classified into three classes: type 1, according to dissolution; type 2, according to layering; and type 3, according to the nature of the API.

- Type 1 ODFs

Type 1 ODFs are divided into three subclasses: fast, moderate, and slow. Films that dissolve within thirty seconds are termed fast-dissolving ODFs and have a thickness of around 50–150 μm; films that dissolve within one to thirty minutes are known as moderately dissolving ODFs; and slow-dissolving ODFs can take more than thirty minutes to dissolve. Fast-dissolving films are used in emergency conditions, while slow/moderately dissolving films are used to prepare nicotine-based products, as they help to lessen or eradicate cravings in patients who have used tobacco regularly and become dependent

- Type 2 ODFs

Type 2 ODFs are classified according to the number of layers they contain. Layers can be monolayers, bilayers, or multilayers. Monolayer oral films consist of an API, a film-forming polymer, and excipients, while bilayer or double layer films consist of one API layer and another taste-masking or permeation-enhancing layer. In multilayer films, the API layer is sandwiched between two layers.

- Type 3 ODFs

Type 3 ODFs are further classified according to API source, which may be synthetic, e.g., sildenafil, or natural (animal or plant), e.g., ginger and turmeric. Films prepared using minerals, vaccines, vitamins, or micronutrients constitute the other class of type 3 ODFs, e.g., vitamin D ODFs. All of these ODFs

contain prescription drugs or over-the counter drugs, while ODFs prepared from plant sources are difficult to fabricate.

IV. CLASSIFICATION OF MOUTH DISSOLVING FILMS [4]

There are three main kinds of mouth dissolving film

1. Mucoadhesive sustained release wafer
2. Mucoadhesive melt away wafer
3. Flash release wafer.

1.Mouth adhesive sustained release wafer:

- It is used on the mouth cavity or gingival tissue.
- Drugs are distributed in suspension or solid solution.
- They use non-soluble polymers.
- Low solubility excipients are utilized.
- Structure with several layers
- Area 2-4 cm2
- Thickness 50-250mm
- Dissolution 8-10h

2. Mucoadhesive melt away wafer:

- It is applied to the buccal or gingival area.
- Medicines that are suspended or dissolved in solid solution
- Polymers that are hydrophilic are necessary
- Use of soluble excipients
- one or more layers of structure
- area 2-7 cm2
- 50–500 mm in thickness;
- 1-3 minutes for dissolving

3.Flash release wafer:

- It is placed on the tongue's top plate.
- The medications are distributed in a solid solution phase.
- Use of a very hydrophilic polymer
- The usage of soluble excipients
- One-layered construction
- Area 2-8cm2
- Thickness: 20–70 mm
- Maximum dissolution time: 60 s.

V. ADVANTAGES OF MOUTH DISSOLVING FILM [6]

- For paediatric, elderly, and psychiatric patients who have trouble swallowing tablets and other solid dosage forms, it is simple to administer.
- No water is required for swallowing.
- Rapidly acting medications that are poorly water soluble that dissolve and absorb quickly.
- Paragastric absorption can lead to improved clinical performance through a decrease in side effects, greater bioavailability with a smaller dosage, and.
- Bitter medications have the potential to be taste-masked.
- Useful in situations requiring a rapid initiation of action, such as motion sickness, an unexpected allergic reaction or coughing
- fit, hypertension, bronchitis, or asthma. More affordable.
- The dosing procedure is simple and precise.
- Reasonable transportation.

VI. DISADVANTAGES [6]

The MDF has several benefits, but a few drawbacks make its formulation particularly difficult.

- Because of its hygroscopic nature, it needs to be stored in dry environments.
- Film packaging is challenging to pack and calls for specialized equipment.
- Special packaging is required because they need to be water-resistant.
- The oral film cannot include a large dosage.
- Restrictions may be placed on eating and drinking.
- It is not possible to provide drugs that are unstable in oral pH.
- To guarantee the stability and safety of the product, special packaging is needed.
- High dose cannot be incorporated into the oral film.

VII. IDEAL REQUIREMENT OF MOUTH DISSOLVING FILM [6,7]

The following is an overview of the optimum conditions for MDF:

- To enable a reliable production and storage process as well as ease of handling and administration, mouth dissolving film should be flexible and thin but stable.
- The films need to be portable, non-sticky, and able to keep their level shape without rolling. Simple administration for people who are mentally ill, disabled, or unwilling.

- They need to taste good and have a pleasing texture.
- No need for water exists.
- It should take as little time as possible for anything to decompose.
- They should be mostly influenced by environmental variables like humidity and temperature.
- They must be able to deliver the advantages of liquid medicine in the form of a solid formulation.
- A unit MDF's size shouldn't be so big that it inhibits the patient's ability to the willingness to accept.
- The MDF should have a uniform, smooth surface and be both physically and chemically stable throughout its shelf life.

VIII. FORMULATION ASPECTS FOR MOUTH DISSOLVING FILMS [2]

Table 1: Composition of mouth dissolving films.

SR. NO.	NAME OF INGRIDIENT	USES	AMOUNT	EXAMPLE
1	Drug	Therapeutic activity	5 -30%w/w	All drugs are suitable
2	Polymer	Ability to forming film	45%w/w	HPMC
3	Plasticizers	Increase flexibility reduce bitterness of film	0-20%w/w	Glycerol, Polytheleneglycol
4	Surfactant	Solubilizing agent &wetting agent	9.5%w/w	Tween 80, SLS
5	Sweetning agent	Enhance the palatability	3-6%w/w	Saccharine, Aspartaine
6	Saliva stimulating agent	Increase saliva stimulation	2-6%w/w	Citric acid
7	Flavours	To mask the odour of drug	Should not exceed 1% w/w	Menthol
8	Colors	To give elegancy to film	Should not exceed 1%w/w	Titanium dionide

IX. . METHODS OF PREPARATION [3-9]

Method of preparation of Mouth dissolving films

Mouth dissolving films can be prepared by:

1. Solvent casting method
2. Semisolid casting method
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method
6. 3D Printing

1. Solvent casting method:

Polymers that are water soluble are dissolved to create a homogeneous solution. Drugs and other water-soluble ingredients are given a little amount of water to dissolve in. Continuous stirring is used to combine the two solutions. Applying a vacuum removes air bubbles that have become entrapped. The produced solution is cast onto Petri dish and then divided into bits.

Advantage:

Great uniformity of thickness & great clarity than extrusion. Films have fine gloss & freedom from defect such a die lines. Films have more flexibility & better physical properties.

Disadvantage:

The polymer must be soluble in a volatile solvent or water. The stable solution with reasonable minimum solid content & viscosity should be formed.

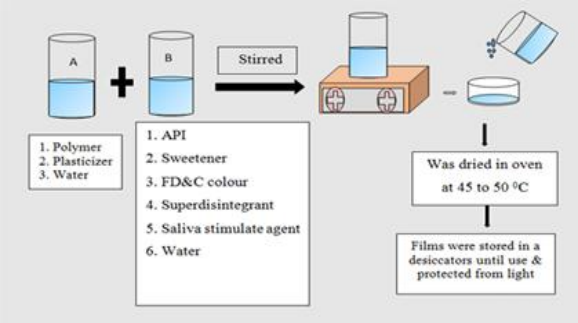

Fig. 2: Solvent casting method.

2. Semisolid casting method:

When water-insoluble polymers are required for the film preparation, this approach is preferred. A gel mass is cast into the films or ribbons using the semisolid casting technique, which uses heat-controlled drums. Gel mass is created by mixing a film-forming solution with an acid-insoluble polymer solution in sodium hydroxide or ammonium hydroxide. The polymers cellulose acetate phthalate and cellulose acetate butyrate are insoluble in acids. The proportion of 1:4 acid insoluble polymer to film-forming polymer should be taken.

3. Hot Melt Extrusion:

Hot melt extrusion is a technique in which a mixture containing drug, polymer and excipients is extruded under high temperature to form a homogenous mass which is then coasted to form smooth films. This is a solvent free process; however, the processing of thermolabile substances is a major drawback of this process due to the use of high temperature during extrusion

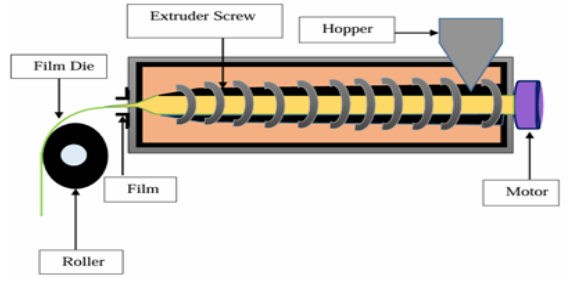

Fig. 3: Hot melt extrusion.

Advantages:

Fewer operation units

Better content uniformity

An anhydrous process

4. Solid dispersion extrusion:

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. In this method drugs are dissolved in suitable solvents and then solutions are incorporated into the melt of polyethylene glycol below 70o C. Then solid dispersions are finally shaped into the films by means of dies.

5. Rolling method:

According to this method, a premix is prepared, an active is added, and then a film is created. Create a premix using a polar solvent, film-forming polymer, and additional ingredients other than a drug. Fill the master batch feed tank with premix. It was fed to either the first mixer or both the first and second mixer using a first metering pump and control valve. Add the necessary amount of the drug to the chosen mixer. To create a homogeneous matrix, combine the drug with the master batch premix. The pan is then supplied with a predetermined quantity of homogeneous matrix using the second metering pumps. Finally, the film is created on the substrate and removed using the support roller. Then, employing controlled bottom drying, the wet film is dried.

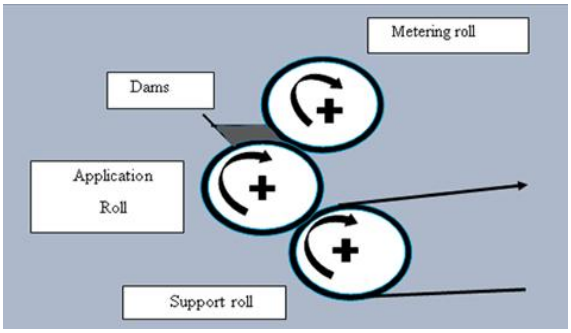

Fig.4: Rolling method

6. 3D Printing:

Over the past few years, researchers have also tried to develop ODFs using a new technique, namely, 3D printing. This is an additive technique that relies on the deposition of different layers of ingredients. Researchers have developed ODFs using 3D printing techniques, and in the final step of production the resultant is formed by the solidification of powder material or semi-solid material or by liquid materials. In 3D printing methods, extrusion technologies with fused deposition are the commonest means of developing drug delivery systems. One example of this method is the fabrication of aripiprazole ODFs. Initially, aripiprazole filaments are prepared by hot-melt extrusion then mixed with PVA and moistened with ethanol before drying. The film filaments are

prepared using an extruder. The blended powder is fed and extruded through the die at a constant speed. The film filament is then collected and further used to fabricate 3D-modeled ODFs. The fabricated ODFs have specific lengths, widths, and depths.

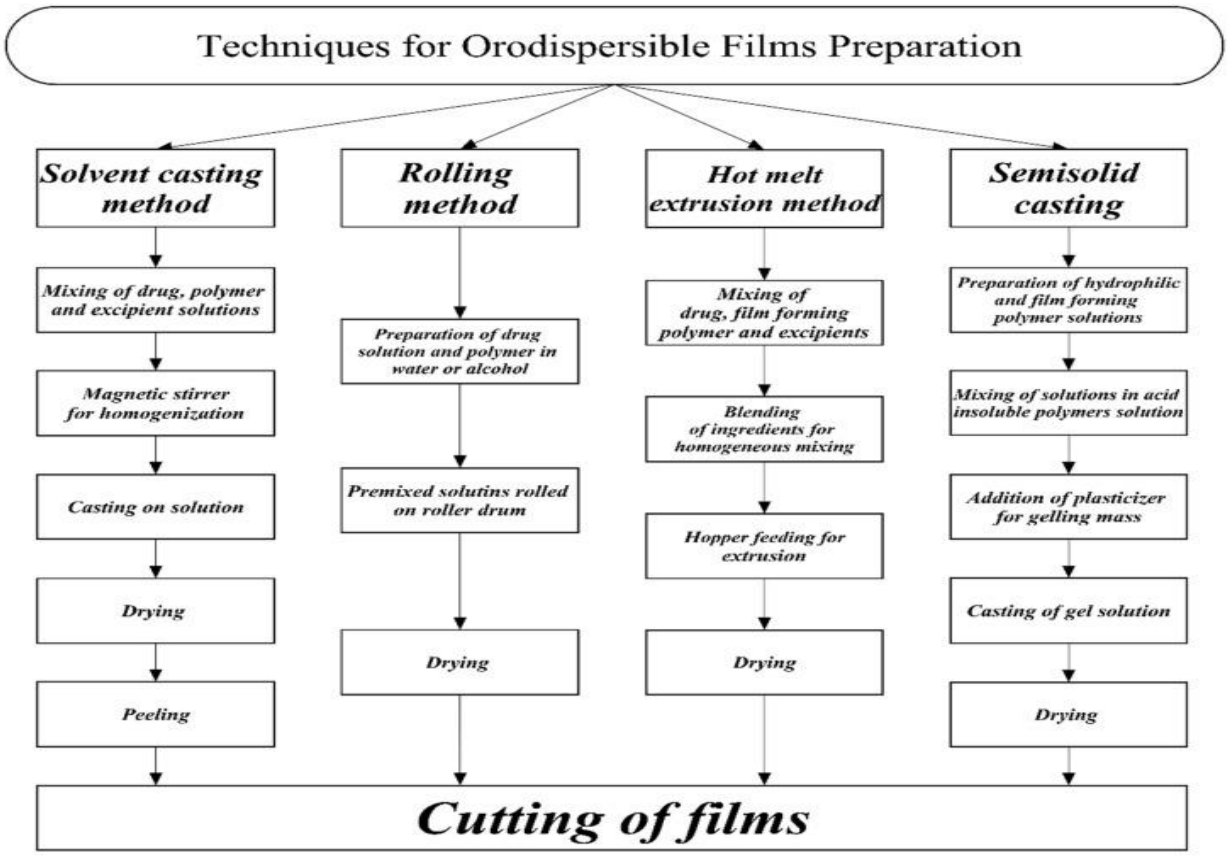

Fig. 5: Flowchart of processes involved in the preparation of mouth dissolving films.

X. EVALUATION PARAMETERS [8-18]

Physical appearance and surface texture (Evaluation of organoleptic properties):

Organoleptic properties such as colour, flavour, and taste should be primarily evaluated. It is mainly done by visual inspection of prepared buccal films. The errors in manufacturing processes can lead to defects in buccal film formulation. This may include defects in the surface texture of films. An uneven surface of buccal films is the indication of non-a-uniformity of contents and fault in developed films. Good taste, colour, and surface texture provide more patient accessibility. The taste of the film can be determined using E-tongue software.

Thickness:

The buccal film should have a uniform and optimum thickness with a range of 5–200 µm. Proper thickness ensures the accurate dose and good absorption of the drug. Thickness can be measured either using an electronic digital micrometre screw gauge or calibrated digital Vernier caliper. To determine the thickness,

different positions such as four corners and the center of a film should be considered.

Weight Variations:

Weight variation is measured by individually weighting randomly selected 10 films. The average weight should not differ significantly from the average weight.

Tensile strength:

Tensile strength is defined as maximum stress applied at which the film breaks. Basically, this test is performed to measure the mechanical strength of films. It can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below

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

Youngs modulus:

It is use to estimate stiffness. It is found as balance applied stress to the strain in the region. it is determined by, Youngs modulus = force of corresponding strain/cross sectional area.

Contact angle:

The contact angle can be measured at room temperature using the Goniometer (AB Lorentz and Wetter, Germny). This can be done by applying a droplet of distilled water to the surface of a dry film. Ten seconds after the water droplets are deposited, images of them are taken with a digital camera. The contact angle can be measured on both sides of the descent, and an average is calculated.

Transparency:

A simple UV spectrophotometer can be used to evaluate the films' transparency. Place the film into the spectrophotometer cell after cutting it into a rectangle. Determine the transparency of the film at 600 nm. The following formula can be used to determine the transparency of the film:

Transparency= (log T600)/b = —єC

Where,

T600= transmittance at 600nm,

b= film thickness (mm)

C= concentration

Percent elongation:

The percent elongation at break was measured by formula given b

Strain (E) = $\frac{\text{Original length}}{\text{Total elongation}} \times 100 = \frac{L - L_0}{L_0} \times 100$

Where, L = l e was ap L0 = original length.

Folding endurance:

Folding endurance of the films was determined by repeatedly folding the small strip of size (2×2 cm²) at the same place till it breaks. The number of times the film can be folded at the similar place without breaking give the value of folding endurance. The three readings average and standard deviation of all films is calculated.

Swelling index:

Buccal films are weighed individually (W1) and placed separately in petri-dish containing phosphate buffer pH 6.8. The buccal films are then removed from the petri dish and excess surface water is removed using filter paper. The buccal films are reweighed (W2) and swelling index (SI) was calculated as follows:

S.I. = (W2-W1)/W1

Whereas:

S.I. = Swelling index

W2 = Final weight

W1 = Initial weight

Surface pH of the film:

After being wet with 1 millilitre of distilled water and held for 30 seconds, the film to be tested was put in a Petri dish. After allowing one minute for equilibration and contacting the formulation's surface with the pH meter's electrode, the pH was measured. For every formulation, an average of three determinations was made.

Moisture content:

The brittleness and friability of films are impacted by the moisture content. In short, the product's ingredients control how much moisture is present in a given film. Generally, moisture content testing equipment, the Karl Fisher titration method, or the weighing method used to determine how much moisture is contained in the film. Usually, a pre-weighed film of a certain size is heated to between 100 and 120 °C until it reaches a consistent weight, and the difference in weight indicates the amount or level of moisture contained in the film. % Moisture content= [(Starting mass - Final mass) 100/Initial weight] used to compute moisture content. The optimal moisture content for a film is 5% or less.

Stability Study:

Stability studies were carried out on formulation, according to ICH guidelines by storing replicates of films (packaged in aluminium foil) in a humidity chamber, with a relative humidity of 75± 5% and a temperature of 40±0.5 °C. At periodic intervals the samples were taken out at 0, 15, 45 and 90 days and the period for their degradation of the film was checked. Samples were also analysed for drug content.

In vitro disintegration time:

For this test, a piece of the film (2 × 2 cm) is carefully placed in a glass petri dish containing 10 ml of distilled water. The time taken for the film to completely break apart into small particles is recorded as the disintegration time. The procedure is repeated for three samples to obtain consistent results.

Test for in vitro dissolution:

The paddle or basket apparatus mentioned in the pharmacopoeias used to conduct dissolution testing.

The sink conditions and API dose will primarily be taken into consideration while choosing the dissolving medium. The tendency of the strip to float onto the dissolving media when the paddle equipment is used frequently makes the dissolution test challenging.

Assay / Uniformity of content:

Standard assay technique specified for the specific drug candidate in the standard pharmacopoeias are used to determine uniformity of content. The consistency of the material is evaluated through determining the API content in every separate film. The maximum content uniformity is between 85 and 115%.

Packaging of Mouth Dissolving Film:

Various packaging options are available for mouth dissolving films, but single packaging is mandatory. The most commonly used packaging material is an aluminium pouch, The mouth dissolving films can be packaged using various methods, including single pouches, blister cards with multiple units, multiple unit dispensers, and continuous roll dispensers. The packaging process involves the use of vertical or horizontal form-fill-seal equipment to create flexible pouches, with single or aluminium pouches being the preferred choice. The pouch may be transparent to allow for product display, with one side being transparent and the other side having foil lamination to prevent the transmission of gas and moisture. Aluminium pouches are the most commonly used packaging option. Blister cards consist of two components: the blister, which holds the product, and the lid stock, which seals the blister.

The ideal properties of material selected for packaging include

- Protection from environmental conditions: The packaging material should protect the product from moisture, light, and other environmental factors that could degrade its quality.
- Approval by FDA: The packaging material must be approved by the FDA for use in pharmaceutical products.
- Non-toxic: The packaging material must be non-toxic and safe for human consumption.
- They must be inert and not react with the product.
- No taste or odor: The packaging should not impart any taste or odor to the product that could affect its acceptability or efficacy.

XI. CONCLUSIONS

This review shows that mouth dissolving films are promising dosage form as they have more patient compliance and rapid onset of action. Moreover, they are potential candidate for oral route as they can deliver drug locally as well as systematically. MDF are used for paediatric and geriatric population or for patient those who have difficulty in swallowing. Due to these advantages MDF used to treat patient efficiently.

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