Mouth Dissolving Films: an innovative approach for drug delivery

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Abstract: Oral formulations are prone to issues such as instability with unpredictable absorption throughout the gastrointestinal tract, first-pass metabolism, and patient-related and pathological dietary challenges. However, there has been a global movement away from traditional dermal formulations toward those that are more aesthetically pleasing. In the midst of all of this, polymeric films and film-forming devices have shown promise as solutions to these difficulties. Fast-dissolving mouth films provide a practical method of administering medication to children, the elderly, and patients who are bedridden; oral films help reduce dosage, improve the medication’s effectiveness and safety profile, and prevent first-pass metabolism.

Key word: Mouth dissolving films, oral mucosa, Polymer, Plasticizer, solvent casting method.

I. INTRODUCTION:
The need for more patient-friendly dosage forms has increased during the past two decades. Recent technological advancements have offered effective dosing solutions for people who might struggle to swallow pills or liquids. According to estimates, 25% of the population has trouble swallowing pills and capsules. As a result, they fail to take their prescription as directed by their physician, which leads to a high rate of non-compliance and inefficient treatment. Drug solutes are quickly absorbed into the reticulated vein when administered sublingually or buccally, as has long been recognized; most medications used to have systemic effects are likely given orally, with the likelihood that this number is at least 90%. The oral route of administration is still the most popular among the numerous routes of administration because of its many benefits, including ease of administration, avoidance of pain, adaptability, and most importantly, patient compliance. The oral strip is one of these relatively recent dosage forms. It is a thin film made of hydrophilic polymers that dissolves quickly on the tongue or buccal cavity. Fast-dissolving drug delivery systems have recently begun to acquire popularity and acceptance as innovative medication delivery systems since they are simple to use and improve compliance. [1]

Mouth dissolving films have a thin, elegant look and can be offered in a wide range of sizes and shapes on the market. They can be taken without water, which is extremely advantageous when travelling, and there is no risk of choking because it disintegrates when placed on the tongue. MDF can be used in the oral mucosa for local, site-specific effects. [2] Mouth dissolving films (MDF) are also known as oral fast dissolving films (FDF), oral strips, and orodispensible films (ODF). When the medicine is ingested after being dissolved or spread in the saliva, it is absorbed normally through the gastrointestinal tract. As saliva travels down into the stomach, certain drugs are absorbed from the mouth, throat, and oesophagus, which may result in a quick onset of action. Since this occurs, the bioavailability of the medications is substantially higher than what is seen with the traditional tablet dosage form. [3]

MDF is better than tablets and liquid since it combines the best qualities of both solid and liquid dosage forms. It demonstrates quick dissolution and good bioavailability as a liquid, and until consumption, it is in a solid state with stability similar to that of a solid dosage form. [4]
The film is developed in the shape of a big sheet, which is subsequently sliced into individual dose units for packaging in a variety of pharmaceutically approved formats. [5]

II. IDEAL CHARACTERISTICS FOR MDF’s: [6, 7]
MDF’s should have the following qualities,
• It must be thin, flexible, and easy to use.
• The size of a unit film shouldn’t be so large as to compromise the patient’s compliance.
• The film’s texture must be consistent and smooth.
• The disintegration rate should be as quick as possible.
• Give the mouth a pleasant sensation.
• Should not leave traces in the mouth.

III. ADVANTAGES OF MDF’s: [6, 8, 9]
• It can be consumed without water.
• No problem of choking.
• It is possible to self-administer without experiencing any pain.
• Rapid onset of action.
• Due to its larger surface area, film disintegrates and dissolves quickly in the oral cavity.

IV. DISADVANTAGES OF MDF’s: [6, 10]
• Drugs that must be consumed in large amounts cannot be incorporated in films.
• For the films, maintaining dose homogeneity is a difficult challenge.
• Drugs that are unstable at saliva pH cannot be used in a film.
• Sensitive to moisture.
• Need specialized packaging.

V. COMPARISON BETWEEN ORALLY DISINTEGRATING TABLET AND MOUTH DISSLOVING FILM: [11, 6]

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Mouth Dissolving Film</th>
<th>Orally Disintegrating Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mouth dissolving films have a greater dissolution rate due to their wide surface area.</td>
<td>Oral tablets dissolve more slowly than oral films because they have a smaller surface area.</td>
</tr>
<tr>
<td>2.</td>
<td>They are more durable than oral tablets.</td>
<td>They are not as durable as mouth dissolving films.</td>
</tr>
<tr>
<td>3.</td>
<td>Mouth dissolving films have higher patient compliance.</td>
<td>Patient compliance is lower with oral tablets compared to mouth dissolving films.</td>
</tr>
<tr>
<td>4.</td>
<td>Suitable for drugs that require a low dose.</td>
<td>Incorporation of a high dose is possible.</td>
</tr>
</tbody>
</table>

VI. CLASSIFICATION OF MOUTH DISSOLVING FILMS: [12]
There are three different subtype of mouth dissolving film:
  i. Flash release wafer.
  ii. Mucoadhesive melt away wafer.
  iii. Mucoadhesive sustained release wafer.

<table>
<thead>
<tr>
<th>Sub-Type</th>
<th>Flash release wafer</th>
<th>Mucoadhesive melt away wafer</th>
<th>Mucoadhesive sustained release wafer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (cm²)</td>
<td>2-8</td>
<td>2-7</td>
<td>2-4</td>
</tr>
<tr>
<td>Thickness (µm)</td>
<td>20-70</td>
<td>50-500</td>
<td>50-250</td>
</tr>
<tr>
<td>Structure</td>
<td>Single layer system</td>
<td>Single or multilayer system</td>
<td>Multilayer system</td>
</tr>
<tr>
<td>Excipients</td>
<td>Soluble, highly hydrophilic polymer</td>
<td>Soluble, hydrophilic polymer</td>
<td>Low/Non-Soluble polymer</td>
</tr>
<tr>
<td>Drug phase</td>
<td>Solid solution</td>
<td>Solid solution or suspended drug particles</td>
<td>Solid solution or suspension</td>
</tr>
<tr>
<td>Application</td>
<td>Tongue</td>
<td>Gingival or buccal region</td>
<td>Gingival</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Maximum 60 seconds</td>
<td>Disintegration within a few Minutes, forming gel.</td>
<td>Maximum 8-10 hours</td>
</tr>
<tr>
<td>Site of action</td>
<td>Systemic or local</td>
<td>Systemic or local</td>
<td>Systemic or local</td>
</tr>
</tbody>
</table>

VII. GENERAL COMPOSITION OF MOUTH DISSLOVING FILMS: [13, 6]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of the Ingredients</th>
<th>Concentration percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Active pharmaceutical ingredient</td>
<td>5-30%</td>
</tr>
<tr>
<td>2.</td>
<td>Film forming polymer</td>
<td>40-50%</td>
</tr>
<tr>
<td>3.</td>
<td>Plasticizer</td>
<td>0-20%</td>
</tr>
<tr>
<td>4.</td>
<td>Saliva stimulating agent</td>
<td>2-6%</td>
</tr>
<tr>
<td>5.</td>
<td>Sweetening agent</td>
<td>3-6%</td>
</tr>
</tbody>
</table>
1. **Active pharmaceutical ingredient:** \cite{11, 14, 6}  
MDF’s technology has the ability to deliver a wide range of APIs. Unfortunately, because the size of the dosage form is limited, high-dose medications are challenging to incorporate into films.

**Ideal characteristics of APIs:**
- Small dose – up to 40 mg.
- Palatability
- Low molecular weight
- Solubility and stability in saliva

2. **Film forming polymer:**

Determining the polymer is a crucial consideration in enhancing the efficiency of film formation. Whether used separately or in combination, polymers play a vital role in achieving the desired film characteristics. \cite{16}

In order to ensure the desired properties of the MDF’s, it is important that the film-forming polymer comprise at least 45% w/w of the total weight of the dry film. However, it is typically preferred to have a higher concentration of polymer, around 60 to 65% w/w, to achieve the desired properties.

Since the film formulation quickly disintegrates and dissolves in the oral cavity, the polymers employed to produce the film must be water-soluble. \cite{14} The water-soluble polymers offer quick disintegration, a pleasant mouth feel, and mechanical properties to the films. The disintegration rate of the polymers is reduced with increasing the molecular weight of polymer film bases. \cite{15}

**Ideal characteristics of the film forming polymer:** \cite{14, 15}
- The polymer used should not be toxic, irritating, or contain any leachable impurities.
- It should have good spreading and wetting properties.
- The polymer needs to have adequate peel, shear, and tensile strengths.
- The polymer has to be widely accessible and cost effective.
- It should have a good mouth feel and not contribute to the development of secondary infections in the dental or oral mucosa.
- The polymer should have a long shelf life.

### Polymers available for preparation of MDF: \cite{15}

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Type of polymers</th>
<th>Example of polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Natural Polymers</td>
<td>Pullulan, Starch, Gelatin, Pectin, Sodium alginate, Maltodextrins, Polymerized Rosin</td>
</tr>
<tr>
<td>2.</td>
<td>Synthetic Polymers</td>
<td>Hydroxypropyl methylcellulose, Sodium Carboxy methyl cellulose, Polyethylene oxide, Hydroxypropyl cellulose, Polyvinyl pyrrolidone, Polyvinyl alcohol</td>
</tr>
</tbody>
</table>

3. **Plasticizer:** \cite{17, 18, 19}

Plasticizer reduces the polymer's glass transition temperature by improving the film's mechanical properties, such as tensile strength and elongation. It also reduces the brittleness of the film, which improves its flexibility. The plasticizer used is determined by the type of solvent used and its compatibility with the polymer. When plasticizer is used inappropriately, it can cause the film to bloom, fracture, split, and peel.

Plasticizers used for MDF’s are phthalate derivatives like dimethyl, diethyl, and dibutyl phthalate, low molecular weight polyethylene glycols, castor oil, citrate derivatives like tributyl, triethyl, acetyl citrate, triacetin, and glycerol.

4. **Saliva stimulating agent:** \cite{20}

The purpose of employing saliva-stimulating agents is to increase the rate of saliva production, which will help the film formulation to disintegrate and dissolve more quickly. In general, acids employed in food preparation can be used as salivary stimulants. Salivary stimulants used in MDF’s are citric acid, tartaric acid, ascorbic acid, lactic acid, and malic acid. Among all acids, citric acid is the most preferred.

5. **Sweetening agent:** \cite{21}

Sweeteners are a significant ingredient in Mouth Dissolving Films. They are commonly used to mask the taste of bitter medications, making them more appealing.

<p>| | | |</p>
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</table>
Natural sweeteners used in MDF’s are sucrose, xylose, glucose, ribose, fructose, dextrose, and maltose. Artificial sweeteners used in MDF’s are ascesulfame k, calcium or sodium saccharine salts, cyclamates salts.

6. Surfactants; [7, 22]
Surfactants are employed as solubilizing, wetting, or dispersing agents, allowing the film to dissolve and release the active substance instantly. When employed in fast-dissolving buccal films, surfactants improve the solubility of poorly soluble drugs. Surfactants used in MDF’s are Poloxamer 407, benzthonium chloride, sodium lauryl sulfate, benzalkonium chloride, tweens and spans.

7. Flavouring agent; [23, 14]
The choice of flavour is influenced by the type of drug to be used. The amount of flavour required to cover up the taste depends on the type and potency of the flavour. They can be employed alone or in combination. Flavouring agents used in MDF’s are sweet confectionary flavours such as chocolate and vanilla. Fruit flavours such as orange and lemon. Intense mints such as clove, spearmint, peppermint, cinnamon, sweet mint, and wintergreen. Fruit essences like pineapple, apple, cherry, and raspberry.

8. Colouring agent; [24]
Colouring agents that are commonly used include FD&C colours, natural colours, pigments such as titanium dioxide, etc.

VIII. METHODS USED IN PREPARATION OF MDF:
1. Solvent casting method
2. Hot-melt extrusion
3. Semisolid casting
4. Rolling method.
5. Solid dispersion extrusion

1. Solvent casting method:
The solvent-casting method is the most preferred method for the formulation of MDF. [26] In this method, water-soluble polymers are first dissolved in water at 1,000 rpm and can be heated up to 60°C. All other excipients, such as colours, flavouring agents, sweetening agents, and so on, are dissolved separately. The obtained solutions are then thoroughly mixed while being stirred at 1,000 rpm. The obtained solution is mixed with the API, which has been dissolved in a suitable solvent. A vacuum is used to remove the trapped air. The resulting solution is cast as a film and allowed to dry before being cut into units of the desired size. [25] The solvent casting method is a hydrous process ideal for thermolabile and thermostable drugs. [26]

2. Hot-melt extrusion; [26, 6]
Before the heating process, the API and other excipients are blended in a dry state. The molten mass is then extruded from the hot-melt extruder. This process has the benefit of complete solvent elimination. Before being cut to size, the films are given time to cool. This process is suitable for thermolabile drugs due to the high temperature used. [26] while temperature-sensitive drugs cannot be used. In comparison to other methods, this method has some advantages, including minimal product waste and better content uniformity. [6]

3. Semisolid casting: [27]
The water-soluble polymer is made into a solution. The resultant solution is mixed with an ammonium or sodium hydroxide soluble polymer (such as cellulose acetate butyrate and cellulose acetate phthalate). To create a gel mass, the correct amount of plasticizer is applied. Using a regulated heat source, the gel mass is cast as films or ribbons. The film’s thickness is maintained between 0.015 and 0.05 inches.

4. Rolling method; [28, 26]
The drug-containing solution or suspension is rolled onto a carrier. Water and a combination of water and alcohol make up the majority of the solvent. The film is dried on the rollers before being cut into the required shapes and sizes.

5. Solid dispersion extrusion: [29]
In this procedure, the drug is initially dissolved in a suitable liquid solvent before being added to a melt of PEG that is below 70°C. The chosen drug or solvent could not mix with PEG melt, and the solvent may have an impact on the drug’s polymorphic form that has precipitated in solid dispersion.

IX. EVALUATION PARAMETERS FOR MDF:
1. Organoleptic evaluation; [25, 31]
Homogeneity, surface smoothness, taste, colour, and flavour are the desirable organoleptic qualities for mouth-dissolving films. Since the film will disintegrate in the mouth, it should possess sufficient organoleptic and appealing properties.

2. Thickness; [32]
A digital vernier caliper is used to measure the thickness of the film at various points. It is necessary to ensure consistency in the thickness of the film since it is directly connected with the accuracy of dosing in the film.

3. Folding endurance; [34]
The folding endurance of the film is tested by repeatedly folding one film at 180° until it breaks. The number of times the film can be folded in the same location without breaking is the folding endurance value.

4. Tensile strength; [35]
Tensile strength is the highest force necessary to break the films. This parameter is used to determine the strength of the films.

\[
\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the film (mm}^2\text{)}}
\]
5. **Percentage elongation:**

It is the percentage ratio of the length increase to the initial length. The following formula is used to calculate percentage elongation.

\[
\text{Percentage elongation} = \frac{[\text{Final length} - \text{Initial length}] \times 100}{\text{Initial length}}
\]

6. **Young's modulus:**

Young's modulus, also known as elastic modulus, is used to determine a film's stiffness.

\[
\text{Young's modulus} = \frac{\text{slope} \times 100}{\text{Film thickness} \times \text{cross-head speed}}
\]

7. **Weight variation test:**

A 1 cm² sample representing five distinct locations on the film is cut, the weight of each film is collected, and the weight variation is determined.

8. **Drug content uniformity:**

Content uniformity is determined by any standard assay method provided for the specific API in any of the standard pharmacopoeias. Content uniformity can be evaluated by estimating the API content in each strip. The limit for content uniformity is 85–115%.

9. **Surface pH:**

To evaluate possible side effects in vivo, the surface pH of a film is assessed. Because an acidic or alkaline pH might irritate the oral mucosa, it is necessary to keep the pH neutral. The pH is measured by bringing the pH meter's electrode into contact with the formulation's surface and allowing it to equilibrate for 1 minute. For each formulation, an average of three readings should be taken.

10. **In vitro disintegration study:**

Disintegrating time is defined as the time (in seconds) at which a film breaks when it comes into contact with water or saliva. The disintegration test is performed by a disintegration apparatus or in a glass dish with 10 ml distilled water, whirling every 10 seconds.

11. **In Vitro dissolution study:**

Dissolution tests are carried out using the basket method (USP 1) and the paddle method (USP 2), with rotating speeds of 50 and 100 rpm, respectively. The solution used for dissolution consists of bi-distilled water or a simulated saliva solution with a pH value of 6.7 and a temperature of 37 ± 1°C maintained. A 5 mL sample solution is taken out at specific time intervals, and the withdrawn volume is replaced with a blank volume.

12. **Stability studies:**

As per ICH norms, films were subjected to 12 months of controlled environmental conditions of 25°C/60% RH and 40°C/75% RH. During storage, the films should be evaluated for changes in their physical characteristics, including mass, tensile properties, reduction in film thickness, water content, and dissolving behaviour.

X. **STORAGE AND PACKAGING OF MDF:**

Mouth-dissolving films can be packaged in a variety of ways, including in single pouches, blister cards containing several units, multiple-unit dispensers, and continuous roll dispensers. For mouth-dissolving films, there are patented packaging technologies such as Rapidcard by Labtec and Core-peel by Amcor Flexible. Rapid cards come in the same size as credit cards and include three film slots on each side. Each dose can be withdrawn independently.

XI. **CONCLUSION:**

MDF formulations are one of the unique techniques in the pharmaceutical sector, and it may become one of the potential dosage forms for illness or condition therapy in the future. These innovative formulas have higher patient compliance and acceptability, as well as greater safety and effectiveness than traditional formulations. MDF has various benefits, including enhanced treatment response. At the moment, these formulations are only accessible for the treatment of a few diseases, but given their relevance, it is possible that further diseases may be treated by developing film formulations with appropriate API.

ACKNOWLEDGEMENT:

We are thankful to the academics and principal of Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Tal. Kalwan Dist. Nashik for their helpful guidance.

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