INTRODUCTION

Diversities of the medicinal inventions are there in the arcade which embraces active components as well as Excipients to create a biocompatible curative product. Pharmaceutical inventions like tablet, capsules, syrups, ointments are extensively acknowledged and believed globally. Therapeutic efficacy of the drug has a prodigious impression on the drug conveyance system. Out of all drug delivery system, oral route is most favored route as they are stress-free to administer, charge effective and suitable to use. The difficulty ascends in the aged, pediatric, bed ridden, non-compliant and woozy patient because of difficulty in swallowing the conservative oral formulations. Throughout the population, 50% of the population was exaggerated by this problem which grades in unproductive therapy. Magnitude of the dosage form, palate and surface form were the mutual criticism concerning the oral dosage form. Travelling patients also agonized from the problem of taking oral dosage form because of un approach ability of water.

History of Fast Dissolving Oral Films

Fast dissolving oral films was first familiarized by North America in 1970. At that period, the oral films were introduced as mouth fresheners and personnel care merchandises. Pfizer was the founder designer of fast dissolving films who entitled it as Listerine® pocket packs™ and it was used as a breath freshener. However, European markets and United States promptly framed fast dissolving films. At this moment there are 15 companies which formulating oral fast dissolving films by ever-changing from formulation of tablet dosage form. The report ascertains that Lab tec GmbH, APR settled a unique technology for the formulation of oral fast dissolving films. In the preceding few years, oral strips get admiration in the breath freshening by rapidly dissolves to discharge minty flavor. Pharmaceutical companies are now making these oral strips as over the counter and prescription pharmaceuticals.

Mechanism of Absorption through Oral Mucosa

For passive drug transference, around two penetration passage ways through the oral mucosa which are Trans cellular (intracellular, passing through the cell) and Para cellular (intercellular, passing around the cell). Drug fragment can use together of the track concurrently however one track is favored over the former depending upon physicochemical possessions of the drug. Cell membrane is lipophilic in nature and has trouble in permeation of hydrophilic solutes because of low partition coefficient. The lipophilic compounds are having little solubility in passive transport system because of the intercellular places which actions as an obstacle to permeation. Meanwhile the oral epithelium is stratified and solute permeation is conveyed by the amalgamation of these two itineraries. Hence, the route which has fewer amount of prevention to passage is favored over the other for permeation through oral mucosa.

Special Features of Mouth Dissolving Film

- Tinny sophisticated film
- Decent mucoadhesion
Accessible in numerous form and extent
Stress-free for administration
No prerequisite of water to swallow
Debauched dissolution and disintegration
Prompt drug freedom
Elude obnoxious perception of the drug
Possibility of clogging and asphyxia throughout oral administration is evaded.
Circumvent first pass result
Leave least or no remainder later the administration.
Afford benefit of liquefied medication in the form of solid preparation.

Limitations of Mouth Dissolving Film
- Drugs which are insecure at buccal pH cannot appropriate.
- Drugs which annoy the oral mucosa can’t be proper for administration by this itinerary.
- High dose range is not allowed for this dosage form.
- Most of the drug have bitter taste and need taste masking.
- Oral films require special packaging because of its fragile nature.
- Dose uniformity is critical challenge.
- Oral films are moisture sensitive.
- This site of administration is not suitable for sustained release dosage form.
- This type of administration interferes with talking, drinking and eating.

Selection Criteria of Drug
- It should have agreeable perception.
- Beneficial dose of the drug has a duty to not more than 40mg.
- The drug should have stump molecular weight and mass.
- The drug had better solubility in water and saliva.
- It ought to be incompletely ionized at pH of buccal cavity.
- The drug has a duty to reveal least sympathy to ecological conditions.
- It should have the talent to pervade the oral mucosa.

Selection Criteria of Polymer
- The polymer should be non-toxic, non-irritant.
- It should having good wetting ability and spread ability.
- Polymer should have sufficient peel and tensile strength.
- The polymer should not very expensive.
- It should be easily available.
- It should not retard disintegration time of the film.
- Polymer should be tasteless.
- Molecular weight of the polymer should not be greater.

Formulation Consideration of Mouth Dissolving Films
The constituents who include in the design of mouth dissolving films are as follow.
- Active pharmaceutical ingredients
- Film forming agent
- Sweetening agent
- Saliva stimulating agent
- Flavoring agent
- Coloring agent
We will deliberate about each ingredient one by one.

Active pharmaceutical ingredients
Drug fragment is the chief element of the film and it covers 1-25% of the film. Numerous categories of active components can be used for the preparation of mouth dissolving film. Lesser dose molecules are the greatest to be merged in the oral films. It is obligatory to cover the acrimonious taste of the drug when the drug is having bitter taste. A number of class of the drug can be incorporated which are antiulcer (omeprazole), antihistamine (salbutamol sulphate), anti-tussives, expectorants and NSAID’s.

Film forming polymer
Hydrophilic and biocompatible polymers are the mainstay of the oral films. The extent of the polymer illustrates the robustness of the film. Polymers used in the formulation are having the prominence for such variety of formulation. The properties like robustness, folding and disintegration time are contingent on the concentration of polymers added into the formulation. Usually 45% w/w of the polymer is used as compared to total mass of the film. The polymers which are having the hydrophilic property are suited for this formulation.

Examples: HPMC E3, E5 and E15, pullulan, sodium alginate etc.
Table 1: Formulations of mouth dissolving films

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of Drug</th>
<th>Film forming polymers used</th>
<th>Plasticizers used</th>
<th>Solvents used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nicotine di picrate</td>
<td>HPMC</td>
<td>Glycerin, PEG 400</td>
<td>Distilled water</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Atomoxetine hydrochloride</td>
<td>HPMC E5</td>
<td>Propylene glycol</td>
<td>Ethanol, Water</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Chlorpromazine</td>
<td>PVA, HPMC E5, HPMC E15,</td>
<td>Propylene glycol</td>
<td>Distilled water</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Tramadol hydrochloride</td>
<td>HPMC E5, HPMC E6,</td>
<td>Polyethylene glycol 400</td>
<td>Distilled water</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Amlodipine besylate</td>
<td>HPMC E3, E5, E15, Microcrystalline cellulose</td>
<td>PEG 400, PVP, SLS</td>
<td>Distilled water, Methanol</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>Donepezil hydrochloride</td>
<td>Sodium alginate, PVP, Guar gum, Cross povidone, Cross Carmelose sodium, Sodium Starch glycolate</td>
<td>Glycerin</td>
<td>Distilled water</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>Acetaminophen</td>
<td>HPMC A5, E5, E15,</td>
<td>Polyethylene glycol 400</td>
<td>Distilled water</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>Aprepitant</td>
<td>Pullulan</td>
<td>Polyethylene glycol 400</td>
<td>Distilled water</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>Diazepam</td>
<td>HPMC E3, E5, E15</td>
<td>Polyethylene glycol 400, Propylene glycol</td>
<td>Methanol and Dichloromethane</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>Dicyclomine hydrochloride</td>
<td>PVA, HPMC E15, HPMC E50: Eudragit HPMC-15:PVA</td>
<td>Polyethylene glycol 400</td>
<td>Distilled water, Ethanol</td>
<td>31</td>
</tr>
<tr>
<td>11</td>
<td>Etoricoxib</td>
<td>HPMC 15 cps</td>
<td>Glycerin</td>
<td>Distilled water</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>Losartan potassium</td>
<td>HPMC 5 cps, Na-Carboxy methyl cellulose, Na-Alginate, Gelatin</td>
<td>Glycerol</td>
<td>Distilled water, Methanol</td>
<td>33</td>
</tr>
<tr>
<td>13</td>
<td>Olanzapine</td>
<td>HPMC E5, Na-CMC</td>
<td>PEG 400, Glycerin</td>
<td>Ethanol 95%, Acetone</td>
<td>34</td>
</tr>
<tr>
<td>14</td>
<td>Ondansetron hydrochloride</td>
<td>HPMC E5, Taro gum,</td>
<td>Glycerin</td>
<td>Distilled water</td>
<td>35</td>
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<tr>
<td>15</td>
<td>Promethazine hydrochloride</td>
<td>HPMC E 15</td>
<td>Polyethylene glycol 400</td>
<td>Distilled water</td>
<td>36</td>
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<td>16</td>
<td>Rofecoxib</td>
<td>HPMC E15, Polyvinyl alcohol</td>
<td>Glycerin, Polysorbate 80</td>
<td>Distilled water, Ethanol</td>
<td>37</td>
</tr>
<tr>
<td>17</td>
<td>Sumatriptan succinate</td>
<td>HPMC E5, E15, Polyvinyl alcohol</td>
<td>Polyethylene glycol 400</td>
<td>Distilled water, Methanol</td>
<td>38</td>
</tr>
<tr>
<td>18</td>
<td>Tadalafil</td>
<td>HPMC E5, E15</td>
<td>Polyethylene glycol 400, Propylene glycol</td>
<td>Distilled water</td>
<td>39</td>
</tr>
<tr>
<td>19</td>
<td>Meloxicam</td>
<td>HPMC E6,</td>
<td>Polyethylene glycol 400,</td>
<td>Distilled water</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>Valsartan</td>
<td>HPMC E5, E50, K4M</td>
<td>Propylene glycol</td>
<td>Distilled water</td>
<td>41</td>
</tr>
</tbody>
</table>

HPMC

HPMC is shortened as Hydroxypropyl Methyl Cellulose. HPMC is a kind of non-ionic cellulose mixed ether. It is a multi-functional polymer used in the pharmaceutical inventions as a thickener, dispersants, emulsifier and film forming agent. It is odorless, tasteless and non-toxic white powder can be dissolved in cold water to precede transparent viscous solution. As film forming polymer in the grounding of oral thin films, it progresses the dissolution proportion of the drugs. HPMC is having good water preservation property and evade cracking of the film. Various grades of HPMC are available in market which is given below44.

Table 2: Pharmaceutical grades of HPMC

<table>
<thead>
<tr>
<th>Type</th>
<th>Viscosity</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>E5</td>
<td>4.5-5.5</td>
<td>2910(E)</td>
</tr>
<tr>
<td>E6</td>
<td>5.6-7.0</td>
<td></td>
</tr>
<tr>
<td>E15</td>
<td>12.1-18.0</td>
<td></td>
</tr>
<tr>
<td>E4M</td>
<td>3000-5000</td>
<td>2208(E)</td>
</tr>
<tr>
<td>K100</td>
<td>91-120</td>
<td></td>
</tr>
<tr>
<td>K4M</td>
<td>3000-5000</td>
<td></td>
</tr>
<tr>
<td>K100M</td>
<td>80000-120000</td>
<td></td>
</tr>
</tbody>
</table>
**Pullulan**

Pullulan is an extracellular polysaccharide created by the fungus Aureobasidium pullulans, used in the food and pharmaceutical industries. It is speedily dissolved in water to form a stable, tacky solution that does not gel. Its solubility can be amended by esterification, etherification or cross linking to make more advantageous formulations. Pullulan solution conveys high asset to paper and wood and stick to inorganic substances such as wood, glass, and metal when smeared and dried out. Pullulan comprehending oral thin films dissolves speedily in warm or cold water three times quicker than PVA films. These films are heat stable and do not misplace its flexibility and elasticity.

**Sodium Alginate**

Sodium alginate gradually soluble in cold water form viscous or colloidal solution. It is insoluble in alcohol and hydro-alcoholic solutions in which alcoholic content is superior to 30% by weight. It is ordinarily used in the formation of mouth dissolving film as a ordinary film former. It has a greater struggle of moisture. It is used as a thickener and emulsifier in a number of preparations.

**Plasticizer**

Plasticizer acts as a chief building block for the preparation of fast dissolving film after the film forming polymer. It organizes 40% of the aggregate weightiness of the film. It supports to progress the elasticity of the oral film and also diminishes the breakability. The mechanical properties of the film are exaggerated by this polymer. Mechanical properties like tensile strength as well as elongation of the film are upgraded by the accumulation of plasticizer.

Examples: Glycerol, Dibutyl phthalate and polyethylene glycols etc.

**Saliva stimulating agent**

The frequency of the creation of the saliva in the oral cavity is amplified by the saliva stimulating agent. It is having the advantage that it raises the disintegration of the film afterward positioned into the oral cavity. Customarily acids are used as saliva stimulating agents.

Examples: Citric acid, malic acid, lactic acid and ascorbic acid etc.

**Colors, flavors and sweeteners**

FD & C sanctioned coloring agents are used for manufacturing of the oral films. Some of the colors added into the formulations are titanium dioxide, silicon dioxide etc.

Flavors are added for fragrance hiding and to upsurge the demand of the film. This is a chief issue for pediatric patients. Peppermint oil and cinnamon oil are the common example of the flavors employed in the pharmaceutical preparations.

Mostly 3-6% w/w of the sweetener is added into the formulation. Sweeteners are auxiliary for the purpose of enlightening the tastiness of the dosage form. Mostly employed sweeteners are saccharin, cyclamate, aspartame and sucralose etc.

**Methods of the Preparation of Mouth Dissolving Film**

**Solvent casting method**

Further most favored direction for the preparation of mouth dissolving film is solvent casting method. In this manner, water soluble constituents are liquefied to form the perfect gummy solution. Active constituents and other agents are liquefied in lesser volumes of solution and then shared with the bulk. Confiscate entrapped air by caring the solution overnight. Resulted solution is casted as film and dried out. At last, cut it into the pieces of the preferred sizes.

**Semisolid casting method**

In this practice, water soluble film forming solution is organized and the consequential solution is added to a solution of acid insoluble polymer (cellulose acetate phthalate) which was prepared in ammonium hydroxide. The suitable quantity of plasticizer is added so that a gel mass is achieved. The resultant solution is casted into the film by consuming heat controlled drums. The proportion of acid insoluble polymer to film forming polymer had better be 1:4.
Hot melt extrusion method

In this scheme, parched constituents are heated as well as homogenized by action of extruder till they are mixed. The igneous material is enforced over and done with flat extrusion die that authorize the material into the favored film shape. Due to hot nature of the material, thickness and strength of the film is exaggerated. The resulted film is cooled, cut and then packed.

![Hot Melt Extrusion Diagram](image)

**Figure 3:** Hot melt extrusion method

Solid dispersion extrusion

Solid dispersion is organized by extruding the immiscible constituents by way of the drug. As a final point solid dispersions are fashioned into the films by means of the dies.

Rolling method

The drug comprehending solution is roll along on a carrier. Customarily water or fusion of water and alcohol is used as a vehicle. The film is dried out into the rollers and cut into the chosen sizes.

Evaluation of Mouth Dissolving Films

Organoleptic evaluation

Color, odor and taste were assessed as an organoleptic property.

Physical appearance and surface texture

Corporeal form was tested by optical scrutiny and outward smoothness was evaluated by way of touch or responsiveness of the film.

Thickness

It was measured through digital vernier caliper with least count of 0.01mm at three altered spots of the film at that moment middling of them was to be deliberated.

Weight variation

Drug content uniformity is straightly concern with the thickness of the drug subsequently it is obligatory to ascertain uniformity in the thickness of the film. It was measured by the micrometer screw gauge or vernier caliper at three unlike spots of the film and the mediocre of the film is to be taken.

Tensile strength

It is nothing but the maximum stress applied to the point at which the strip specimen disrupts.

\[
\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}}
\]

Percent elongation

As soon as stress is applied, a strip model expanses and this is mentioned to a strain. A strain is ultimately the deformation of the strip divided by means of the original dimension of the sample.

\[
\text{Percent elongation} = \left(\frac{L - L_0}{L_0}\right) \times 100
\]

Where \(L\) was the Final length and \(L_0\) was initial length.

Principally, elongation of the strip improves as the plasticizer content upsurges.

Folding endurance

It is determined by the continual folding of the strip at the identical point till the strip disrupts. The figure of folding deprived of breaking is deliberated as folding endurance value.

Surface pH

The films were permissible to swell in secure petri plate at room temperature for 30 minutes in 1 ml of distilled water. Solution was positioned underneath the digital pH meter to conclude the surface pH.

Disintegration time

It elaborates knowledge about the disintegration physiognomies of the film. The obligatory size of the film was positioned in a beaker encompassing 25 ml of pH 6.8 simulated salivary fluids. The time taken by the film to disrupt and liquefied into the fluid is to be measured as in vitro disintegration time.

In vitro dissolution studies

This learning for altogether the consignments of the film was accomplished for five minutes and every single film was positioned with the assistance of forceps in a 50 ml glass beaker covering 30 ml of simulated salivary fluid pH 6.8. Dissolution medium was reserved at 30 °C ± 0.5 °C and magnetic stirrer was rotated at 50 rpm. The sample (5 ml) was withdrawn at 15 seconds, 30 seconds, 1, 2, 3, 4, 5 minutes and switched with renewed simulated salivary fluid pH 6.8. The models were scrutinized for the drug released using UV visible spectrophotometer.

Drug content

It can be experienced by the UV Visible spectrophotometer. Films of every consignment was located in different 100 ml volumetric flask and can be liquefied using the pH buffer and bulk was made up to 100 ml. 5 ml of sample was withdrawn and shifted to 10 ml volumetric flask and bulk was made up to 10 ml. The absorbance of the resultant solution is measured in contradiction of blank in UV spectrophotometer. The percentage drug content was determined using the standard graph. The mean and standard deviations were premeditated.
CONCLUSION

Recently, fast dissolving films have multiplied admiration as dosage forms for the mouth fresheners. In the intervening time, pharmaceutical industries have renamed their prospective for delivering curative products and have thrown several products for the OTC market by consuming this technology. Mouth dissolving films are a very appropriate dosage form for youngsters and the elderly, as they are relaxed to swallow and encompass no possibility of choking. Mouth dissolving films have superior patient agreement and may advance biopharmaceutical properties, improve usefulness and better safety, compared with unadventurous oral dosage forms. The main downside is with drug loading. Drug loading is generally narrow to roughly 40 mg. This problem can be unraveled by increasing the thickness of the film, but that in turn may increase the disintegration and dissolution time. Due to nonexistence of standard methodology for preparation and analysis products existence in the market is limited.

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