Mouth Dissolving Films: Innovative Vehicle for Oral Drug Delivery

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ABSTRACT
Mouth dissolving film becomes a novel approach to oral drug delivery system as it provides convenience and ease of use over other dosage forms such as orally disintegrating tablets buccal tablets and sublingual tablets, so mouth dissolving films are gaining the interest of large number of pharmaceutical industries. Mouth dissolving film was developed on the basis of technology of transdermal patch. Mouth dissolving films are thin solid dosage forms which when placed in the oral cavity; dissolve within few seconds without chewing and intake of water. The oral buccal mucosa being highly vascularized, drugs can absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect. These films offer convenient way of dosing medication to pediatric, geriatric and bedridden patients. The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing and enhance the efficacy and safety profile of medicament. An ideal film should have the properties like pleasant taste, high stability and ease of handling. Present review provides an account of various formulation methods and their evaluation used in film formulations and applications of mouth dissolving film.

Keywords: Applications, components, evaluation, methods of preparation, packaging

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INTRODUCTION
Mouth dissolving films offers an elegant route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage. Also, large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and selective site for systemic drug delivery [1-2]. Recent developments in the technology have presented viable dosage alternatives from oral route for wide variety of group of patients. Buccal drug delivery has lately become an important route of drug administration. Various Bioadhesive mucosal dosage forms have been developed [3]. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experienced difficulties in swallowing traditional oral solid-dosage forms [4]. The novel technology of oral fast-dispersing dosage forms is also known as fast dissolve, rapid dissolve, rapid melt or quick disintegration. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing or fast-dissolving dosage form [5].

The concept of oral dissolving film:
- This delivery system consists of a thin film.
After placing it on the top of the tongue, the film dissolves within seconds, avoiding first pass metabolism and may increase the bioavailability of drug [6].

Accessibility of larger surface area leads to quick disintegration and dissolution in the oral cavity within seconds due to rapid wetting by saliva [7].

Oral dissolving film is flexible so they are not as fragile and need not any kind of special package for protection during transportation and storage as compared to fast dissolving tablets.

No need of water has led to better satisfactoriness amongst the dysphasic patients and to better acceptance during travelling without carrying water.

No fear of choking as compared to fast dissolving tablets.

The large surface area available in the film dosage form allows rapid wetting by saliva then quickly disintegrates and dissolve and absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and on increase the bioavailability[8].

The dosage form can be consumed at any place and any time as per convenience of the individual.

The first pass effect can be avoided, so a reduction in the dose which can lead to reduction in side effects associated with the molecule [9].

Patients suffering from dysphagia, repeated emesis, hypertension, heart attack, asthma, motion sickness, paralysis and mental disorders prefer this dosage form as they are not capable to swallow large quantities of water. Fast dissolving oral films have advantages like, more stable, durable and quicker than other conventional dosage forms; avoid first pass metabolism [10], pleasant mouth feel, accurate dosing, and rapid onset of action and no need of water with patient compliance. Moreover ease of handling and transportability [11].

COMPOSITION OF THE SYSTEM
Mouth dissolving film is a thin film with an area of 2-8 cm² containing an active ingredient. The immediate dissolution, in water or saliva is reached through a special matrix from water-soluble polymers. Drugs can be incorporated up to a single dose of 30mg.

Components of mouth dissolving film includes:

1) Active Pharmaceutical agents:
Active pharmaceutical substance can be from any class of pharmacologically active substances that can be administered orally or through the buccal mucosa. It includes antiulcers, antiasthmatics, antitussive, antihistaminic, antiepileptic, expectorants, antianginal etc. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). Various categories of drugs such as antiemetic, neuroleptics, cardiovascular agents, analgesics, antiallergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorants and anitussive [12-19].

The ideal characteristics of a drug to be selected are as follows:-

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose generally less than 30mg.
- The drugs with smaller and moderate molecular weight should be preferable.
- The drug has should be stable and soluble in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue

2) Water soluble polymers:
The water-soluble polymers achieve rapid disintegration, good mouth feel and mechanical properties to the films. The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases. Some of the water soluble polymers used as film former are HPMC E-3 and K-3, Methyl cellulose A-3, A- 6 and A-15, Pullulan, Carboxymethyl-cellulosekol 30, Polyvinylpyrrolidone PVP K-90, Pectin, Gelatin, Sodium alginate, Hydroxypropylcellulose, Polyvinyl alcohol, Maltodextrins and Eudragit-RD10. Polymerized rosin is a novel film forming polymer [9, 20].

3) Plasticizers:
Formulation considerations (Use of plasticizer) have been reported as
important factors affecting mechanical properties of films. The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties. The commonly used plasticizers are glycerol, di-butyl phthalate and polyethylene glycols etc.

4) Saliva Stimulating Agent:
More saliva production helps in the faster disintegration of the fast dissolving film formulations. So the formulations should contain acids which are used in the preparation of food as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them [21].

5) Flavouring agents:
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. Flavors can be used alone or in the combination. Any flavor can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavor such as lemon, orange or sweet confectionary flavors such as vanillin, chocolate, or fruit essence like apple, raspberry, cherry and pineapple. The amount of flavor needed to mask the taste depends on the flavor type and its strength [22].

6) Sweetening agents:
Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical sources of sweetener are sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. The artificial sweeteners have gained more popularity in pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by ascesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners [23-24].

7) Coloring agents:
FD & C approved coloring agents are used (not exceeding concentration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films, eg. Titanium dioxide [8].

8) Surfactants:
Surfactants act as solubilizing or wetting or dispersing agent in formulation so the film gets dissolved within seconds and releases active agent quickly. Some of the commonly used surfactants are sodium laurel sulfate, benzalkonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing wetting and Dispersing agent [25].

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Amount(s) (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug(API)</td>
<td>5-30%</td>
</tr>
<tr>
<td>2</td>
<td>Water soluble polymer</td>
<td>45%</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>Surfactant</td>
<td>Q.S.</td>
</tr>
<tr>
<td>6</td>
<td>Sweetening Agent</td>
<td>3-6%</td>
</tr>
<tr>
<td>7</td>
<td>Flavours, Colours, Fillers</td>
<td>Q.S.</td>
</tr>
</tbody>
</table>

METHODS OF PREPARATION
One or more of the following process can be used to manufacture the mouth dissolving films
1) Solvent casting
2) Semisolid casting
3) Hot melt extrusion
4) Solid dispersion extrusion
5) Rolling methods

1) Solvent casting method:
In solvent casting method excipients are dissolved in water, then water soluble polymers added in it and lastly drug is added and mixture is stirred to form homogeneous solution. Finally solution is casted in to the petri plate and dried [22, 24].
2) Semisolid Casting:
In this method, solution of water soluble film forming polymer is mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate and cellulose acetate butyrate). After sonication, it is coated on non-treated casting film. On drying the thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4 [22, 24].

3) Hot Melt Extrusion:
In hot melt extrusion method, firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture and finally the melt is shaped into films by the dies. There are certain benefits of hot melt extrusion which includes:
- Fewer operation units
- Better content uniformity
- An anhydrous process

4) Rolling Method:
In rolling method, a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted into desired shapes and sizes. Other ingredients including active agent are dissolved in small portion of aqueous solvent using high shear processor. Water soluble hydrocolloids dissolved in water to form homogenous viscous solution [26].
EVALUATION

1) Thickness:
As the thickness of film is directly concerned with drug content uniformity, it is necessary to ascertain uniformity in the thickness of the film. It can be measured by micrometer screw gauge or calibrated digital vernier calipers at different strategic locations [8].

2) Tensile strength:
Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below.

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

By using above equation tensile strength of film can be calculated [8].

3) Young's modulus:
Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation. It is represented as follows-

\[
\text{Young's modulus} = \frac{1}{\text{Cross sectional area}} \times \frac{\text{Force at corresponding strain}}{\text{Corresponding strain}}
\]

4) Folding endurance:
Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value [8].

5) Disintegration time:
Disintegration of orally fast dissolving films requires U.S.P. disintegration apparatus. The disintegration time limit of 30 seconds or less for orally disintegrating tablets described in C.D.E.R. guidance can be applied to fast dissolving oral strips. Disintegration time will vary depending on the formulation but typically the disintegration range from 5 to 30 seconds. Although, no official guidance is available for oral fast disintegrating films [8].

6) In vitro drug release:
Dissolution studies of films are performed by U.S.P. XXII type II apparatus in 6.8 phosphate buffer (500ml) and 0.1N HCl (500ml). The temperature required is 37±0.5°C and the rotation speed should generally 50 rpm. The samples are needed to withdrawn at various time intervals and should analyze spectrophotometrically [8].

PACKAGING
In the pharmaceutical industry, it is vital that the package selected adequately should preserve the integrity of the product. Expensive packaging, specific processing and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films. An aluminum pouch is the most commonly used packaging format [27].

The material selected for packaging must have the following characteristics:
- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must meet applicable tamper resistant requirements.
- They must be non-toxic.
- They must not be reactive with the product.
- They must not impart to the product taste or odour.

1) Foil, paper or plastic pouches:
The flexible pouch is a packaging concept capable of providing not only a package that is temper-resistant, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling or sealing.
equipment. The pouches can be single pouches or aluminum pouches.

2) Single pouch and Aluminum pouch:
Soluble film drug delivery pouch is a peelable pouch for "quick dissolve" soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminum pouch is the most commonly used pouch.

3) Blister card with multiple units:
The blister container 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. The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mold. After cooling the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminum foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture [27].

Figure 4: Blister card

APPLICATIONS OF FAST DISSOLVING FILM
1) Topical applications:
The use of dissolvable films may be feasible in the delivery of active agents such as analgesics or antimicrobial ingredients for wound care and other topical conditions.

2) Gastro retentive dosage systems:
Dissolvable films are being considered in dosage forms for which water-soluble and poorly soluble molecules of various molecular weights are contained in a film format. Dissolution of the films could be triggered by the pH or enzyme secretions of the gastrointestinal tract and could potentially be used to treat gastrointestinal disorders.

3) Diagnostic devices:
Dissolvable films may be loaded with sensitive reagents to allow controlled release when exposed to a biological fluid or to create isolation barriers for separating multiple reagents to enable a timed reaction within a diagnostic device.

CONCLUSION
The oral route is most popular route for the administration of therapeutic agents by mouth dissolving film because of the low cost of therapy and ease of administration which lead to increase in patient compliance. The mouth dissolving film are barely described and investigated in literature, but seem to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Mouth dissolving oral films has several advantages over the conventional dosage forms. So they are of great importance during the emergency cases such as allergic reactions and asthmatics.
attacks whenever immediate onset of action is desired. And more importantly, mouth dissolving films are travel friendly dosage forms where water may not be carried by person or patient. And hence, mouth dissolving film becomes unique, elegant, selective and needful dosage form.

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