Review Article CODEN: IJPRNK ISSN: 2277-8713
Jui Trivedi, IJPRBS, 2014; Volume 3(1): 149-161 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

MOUTH DISSOLVING FILM: A NEW ERA IN PHARMA FIELD AS A CONVENTIONAL DOSAGE FORM: A REVIEW

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Accepted Date: 02/01/2014; Published Date: 27/02/2014

Abstract: The oral route is most popular route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. The most popular oral solid dosage forms are tablets and capsules. Many patients find it difficult to swallow tablets and hard gelatin capsules particularly pediatric and geriatric patients and do not take their medicines as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. When put on the tongue, this film dissolves instantaneously, releasing the drug which dissolves in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such case is enhancing drug bioavailability, No risk of chocking, Provide good mouth feel. Fast dissolving drug delivery system to overcome this problem difficulty in swallowing tablets/capsules etc. this review article is about general introduction to new innovative drug delivery system as a Mouth Dissolving Film.

Keywords: Fast Dissolving Film, Hydrophilic polymers, Solvent casting, Rolling

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How to Cite This Article:

Jui Trivedi, IJPRBS, 2014; Volume 3(1): 149-161

PAPER-QR CODE

INTRODUCTION

Fast-dissolving buccal film drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and neutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. There are multiple fast-dissolving over the counter and prescribed products on the market worldwide, most of which have been launched recently. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

Fast dissolving buccal films use a dissolving film to administer drugs via absorption in the mouth (buccal or sublingually) and/or via the small intestines (enterically). A film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Fast dissolving buccal films drug delivery has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and over the counter medications. Similar in size, shape and thickness to a postage stamp, thin film strips are typically designed for oral administration, with the user placing the strip on or under the tongue or along the inside of the cheek. Different buccal delivery products have been marketed or are proposed for certain diseases like trigeminal neuralgia, meniere's disease, diabetes and addiction. Improved patient compliance is a primary benefit of the fast-dissolving drug delivery systems. Other benefits of fast-dissolving films include ease of swallowing [1], no water necessary for administration, and accuracy of dosage. This fast-dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment. These additional, superior benefits allow patients to take their medication anytime and anyplace under all circumstances. The fast dissolving buccal film drug delivery system offers a giant leap forward in drug administration by providing a new and easy way of taking medication. Many fast-dissolving tablets are soft, friable, and/or brittle (such as the lyophilized dosage forms) and often require specialized and expensive packaging and processing. These tablets are either very porous or inherently soft-molded matrices, or tablets compacted at very low dissolution/disintegration time. The delivery system is simply placed on a patient's tongue or any oral mucosal tissue [2]. Instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oral mucosal absorption or with formula modifications, will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed.

Overview of Oral Mucosa: [3, 4, 5]

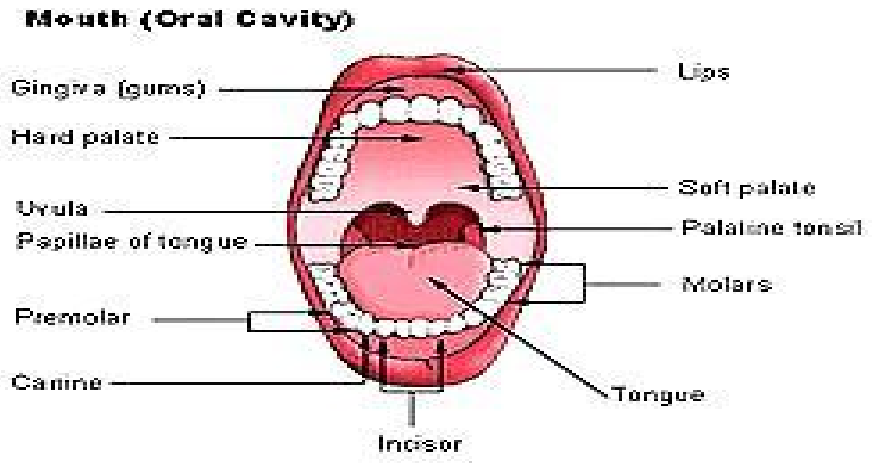

Figure 1: Overview of Oral Mucosa

Drug delivery via the oral mucosa is a promising route, when one wishes to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism. Thus, there is a growing interest in developing alternative dosage forms, i.e. orally fast disintegrating strip, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids. However, in addition to formulation considerations, the properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intraoral administration. The oral mucosa is composed of an outermost layer of stratified squamous epithelium below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer.

Criteria for Mouth Dissolving Film: [6, 7]

Fast dissolving film should

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking
- Have a pleasant mouth feel.
- Allow the manufacture of the tablet using conventional processing and packaging Equipments at low cost
- Leave minimum or no residue in the mouth after oral administration.

- Exhibit low sensitivity to environmental conditions such as temperature and humidity.

Advantages of MDF: [6, 7, 8]

- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling
- Ease of administration to pediatric, geriatric, bedridden patients and psychiatric patients who refuse to swallow tablets.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, which enhances bioavailability of drugs.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improved clinical performance through a reduction of unwanted effects.
- Useful in cases where a rapid onset of action required such as in motion sickness, sudden episodes of allergic attack or coughing, bronchitis or asthma.

Disadvantages of MDF:

1. It is hygroscopic in nature so it must be kept in dry places.
2. It also shows the fragile, granule property.
3. They require special packaging for the products stability and safety
4. High dose cannot be incorporated into the oral film.

Development of Oral Solid Dosage Form:

Various stages of development of the of oral solid dosage formulation [9].

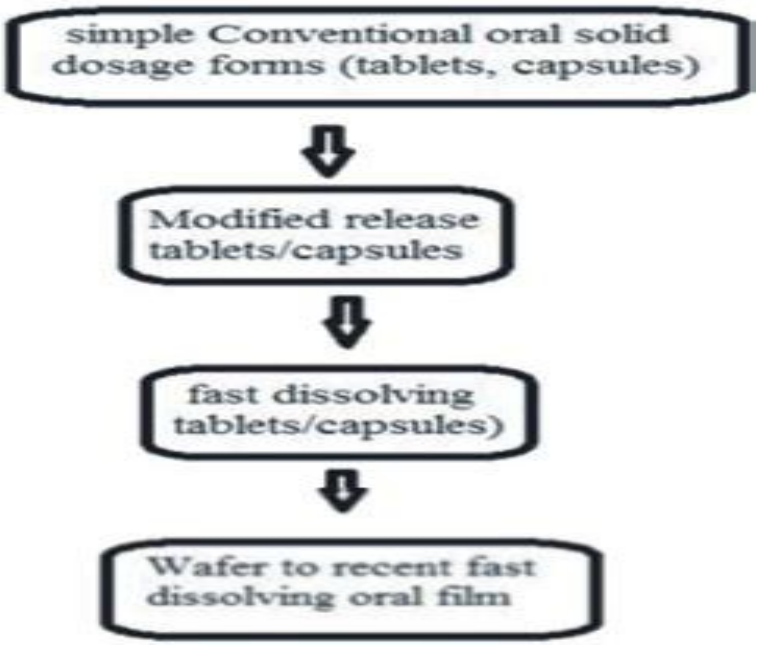

Figure 2: Development of Oral Dosage Form

Formulation of Mouth Dissolving Film:

The area of drug loaded MDF should be between 1-20cm^2. The drug can be loaded up to a single dose of 30mg.

All excipient used in the fast dissolving film should be generally regarded as safe (GRAS-listed) and authorized for use in oral strip. Formulation considerations have been reported as important factors which affected mechanical properties of the films [10].

A Typical formulation containing:

Table 1: A typical formulation of mouth dissolving film

S. No.	INGREDIENTS	AMOUNT (w/w)
1.	Drug	1-30%
2.	Film forming polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva stimulating agent	2-6%
5.	Sweetening agent	3-6%
6.	Flavouring agent	q.s.
7.	Surfactant	q.s.
8.	Colour, filler	q.s.

1. Drug (Active Pharmaceutical Ingredient):

Suitable drug candidate for MDF should possess:

- No bitter taste.
- Good stability in water and saliva.
- Dose should be low as possible.

Various categories of drugs such as antiemetic neuroleptics, cardiovascular agents, analgesics, ant allergic, antiepileptic's, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, antialzheimers, expectorents, anitussive [11,12,13,14]

2. Film Forming Polymers:

Polymers are the most important ingredient of the oral fast dissolving film. Robustness of the film depends on the amount of polymer added in the oral strip. These polymers are mostly attracted considerable attention by medical and neutraceutical industry. Generally 45% w/w of polymer is used which is based on total weight of dry film. Mainly hydrophilic in nature.

Table 2: Polymers used in preparation of Mouth dissolving film:

Sr. no	Natural polymer	Synthetic polymer
1	Pullulan	HPMC
2	Starch gelatin	PVP
3	Pectin	PVA
4	Sodium alginate	CMC
5	Maltodextrin	Polyethylene oxide
6	Polymerized resin	Koll coat
7	Lycoad LG 73	HPC
8	Xanthan	HEC

3. Plasticizer: [15,16]

The role of Plasticizer is beneficial for preparation of FDF. Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the film. The plasticizer should be compatible with polymer and solvent the flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer.

Propylene glycol (PG), Poly ethylene Glycol (PEG), Glycerol, Phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer. Plasticizer may lead to film cracking, splitting and peeling of the film 2.It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug23 .The Plasticizer should be volatile in nature.

4. Flavorant [15]

Flavorant includes:

- Both natural and artificial flavour such as artificial vanilla, cinnamon, and various fruit flavours; either individual or mixed.
- Mints such as peppermint, menthol.
- Essential oils such as thyme, eucalyptol and methyl salicylate.

5. Sweeteners [15,17]

Sweeteners include both natural and artificial sweeteners as:

- Natural sweeteners include monosaccharide's, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolysed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol and mixtures thereof;

- Water-soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and the like and free acid form of saccharin and dipeptide based sweeteners. Aspartame, Neotame are successfully use for the taste masking [18]

6. **Saliva stimulating agent**: [15, 19]

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the FDF. Generally acids which are used 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. These agents are used alone or in combination between 2 to 6% [18]

Methods of manufacture of mouth dissolving films:

One (or a combination) of the following processes may be used to manufacture the oral films:

1. Solvent casting

2. Hot-melt extrusion
3. Semisolid casting
4. Solid dispersion extrusion
5. Rolling.

1. Solvent Casting:

Fast dissolving buccal films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

2. Hot melt extrusion:

Hot metal extrusion is commonly used to prepare granules, sustained release tablets, transdermal and Tran's mucosal drug delivery systems [20]. Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971.

3. Semisolid casting:

Water soluble polymers are dissolved in water

Solution added to solution of acid insoluble polymer (CAP, CAB) which was prepared in NH4OH, NaOH.

Plasticizer is added to obtain gel mass.

The prepared gel mass is cast into films.

Thickness: 0.015-0.05 inch

4. Solid dispersion extrusion:

The term solid dispersions refer to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers.

- Drug is dissolved in a suitable liquid solvent
- Then solution is incorporated into the melt of polyethylene glycol, obtainable below 70◦ C
- Finally the solid dispersions are shaped into the films by means of dies.

5. Rolling method:

A solution or suspension containing the drug is rolled on a carrier.

Solvent: water or water and alcohol

The film is dried on the rollers and cut into desired size.

Evaluation Parameters: [15, 21, 22, 23]

1. Strip thickness measurement

The thickness of the fast dissolving film (2 × 2 cm) was measured using film thickness tester (Mitutoyo, Japan). The thickness of each strip was tested at three different positions.

2. Folding endurance study

It was measured manually for the prepared fast dissolving film (2 × 2 cm). A strip was repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

3. In-vitro disintegration study

Disintegration test was performed in the USP disintegration time testing apparatus (Electrolab, Mumbai). Phosphate buffer (pH 6.6) was used as medium. The films were placed in the tubes of the container and disintegration time was recorded.

4. In-vitro dissolution study

The dissolution test was performed according to the USP type II basket apparatus. Test solution was 900 mL of phosphate buffer (pH 6.6) at 37±0.5°C with a rotation rate of 50 rpm. 10 ml aliquots of samples were taken at time intervals from 1 to 30 min and the same volume of fresh of phosphate buffer (pH 6.6) was replenished. Drug concentrations were assayed spectrophotometricaly. The results were expressed as mean of three determinations.

5. Surface pH study

The surface pH of fast dissolving strip was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral strip was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The experiments were performed in triplicate, and average values were reported.

6. Palatability study:

All the subjects were completely informed concerning the pertinent details and the purpose of the study. A written consent form was supplied, understood, and signed by each subject prior to dispensing the test materials. Films were randomly administered to healthy human volunteers between age group 20–40 years (n = 6; 4 males and 2 females) at 15 min time intervals. A specimen of 4 cm2 was placed in the oral cavity by the volunteer, directly on the tongue. All the subjects were asked to evaluate fast dissolving strips on the basis of three parameters: taste, after bitterness, and mouth feel.

7. Tear Resistance:

The maximum force required to tear the film is recorded as the tear resistance Value. It is expressed in Newton or (pounds –force).

8. Transparency:

The measurement of the oral film transparency can be determined by using a simple UV spectrophotometer. Cut the film sample into rectangles and placed on the internal side of the spectrophotometer cell. Now determine the transmittance of the film at 600 nm.

CONCLUSION

Fast dissolving buccal films have gained popularity because of better patient compliance, rapid drug delivery system, drug is directly absorbed into systemic circulation, first pass metabolism and degradation in gastrointestinal tract can be avoided. Fast dissolving buccal films can be a better option to optimize therapeutic efficacy of various active pharmaceutical ingredients in the future.

Table 3: List of marketed preparations of mouth dissolving film: [24, 25, 26]

S. No	Product	Brand name	Manufactured by
1	Dextromethorphan HBr (cough suppressant), Diphenhydramine Citrate(cough and cold), Breath Strips	Delsym, DexAlone	MonoSolRx
2	Doneprezil rapid dissolving films, Ondansatron rapid dissolving films	Zofran.	Labtec Pharma

3.	Life-saving rotavirus vaccine to infants		Johns Hopkins undergraduate Biomedical engineering
4.	Methylcobalamin fast dissolving films, Diphemhydramine HCl fast dissolving films, Dextromethorphan fast dissolving films, Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films	Methicol, Benadryl, Delsym, DexAlone.	Hughes medical corporation
5.	Altoid cinnamon strips, Boots vitamin c strips, Cool shock peppermint strips, Benzocaine films, Caffeine films		Dow chemical company
6.	Listerine Pocket Paks Breath Freshening Strips		Pfizer's Warner-Lambert

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