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Review Article

FORMULATION AND EVALUATIONS OF MOUTH DISSOLVING FILM USING NATURAL EXCIPIENTS

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Abstract

Mouth dissolving film (MDFs) is the latest oral solid dosage form because of its easy-to-use properties. When mouth dissolving films are placed in mouth, it disintegrates and dissolves within a minute without consuming water or chewing. This dosage form has added advantage as it allows the medication to bypass the first pass metabolism, so bioavailability of medication may be enhanced. Mouth dissolving film has capability to enhance onset of action, lower the dosing and eliminate the fear of chocking. Over the past years, MDFs have appeared as effective oral care products as dosage forms for delivering vitamins, in the form of breath strips, and personal care products. Today fast dissolving films are viewed as latest options for enhanced systemic delivery of poorly absorbed drugs as well. Formulation of mouth dissolving films involves both the visual and performance characteristics as plasticized hydrocolloids, API, taste masking agents are being laminated by solvent casting and semisolid casting method. Nowadays, Mouth dissolving films are also prepared by using natural excipients. Natural polysaccharide extracted from tubers of *Colocassia esculenta* (also called as taro gum) has been utilised as a polymer for film formulation along with semisynthetic polymer HPMC (Hydroxy propyl methyl cellulose). Also, the films using established natural polymers namely xanthan gum, guar gum, gum ghati and sodium alginate are formulated in combination with HPMC. The natural polymers are comparatively cheaper with desired properties like abundantly availability, non-irritating and non-toxic in nature. The utilisation of natural polysaccharides contributes to favourable changes in different properties like disintegration time, tensile strength, and *In-vitro* drug release. This review gives an idea about formulation techniques, evaluation parameters, overview on packaging and some available marketed products of mouth dissolving films.

Keywords: Mouth dissolving film, MDF, solvent casting, fast disintegration, natural excipients.

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INTRODUCTION

Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many alternatives have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance patients[1,2]. Buccal route is a most preferred route of administration for some drugs whose access to the blood is limited by many factors when administered per-oral. Oral mucosa is permeable to a large number of drugs and is largely vascularized which makes it a preferred route for drug administration and has gained attention since recent years[3,4,5].

The drug enters directly into the bloodstream through the oral mucosa, and hence onset of action is rapid compared to per-oral route[5]. Bioadhesive mucosal dosage forms including adhesive tablets, gels and patches are outcomes of technological development. Among various dosage forms, the utilisation of polymeric films for delivering medication into buccal cavity has developed great potential in recent area. These systems were developed in late 1970 to serve as an optional to conventional dosage forms, moreover, fast disintegrating tablets and capsules for geriatrics and pediatric patients having difficulty in swallowing conventional dosage forms[2,6,7]. Fast-dissolving drug delivery systems like fast dissolving films are rapidly gaining interest in the pharmaceutical industry. These systems are either dissolve or disintegrate generally within a minute, without needing water or chewing[8].

In market place, the introduction of MDFs was associated with counseling of patients about the correct administration by giving instruction like ‘‘do not chew/do not swallow’’. However, in spite of these instructions, incidents regarding chewing and swallowing were often reported. But, MDFs untied the masses from these adverse events.

Mouth Dissolving Films can be produced by either solvent cast methods or hot-melt extrusion technology. The solvent casting method suffers from several disadvantages over the hot melt extrusion method due to the solvent residues within the film and the environmental risks in the case of organic solvents[9]. Mouth dissolving films (MDF) disintegrate or dissolve within the oral cavity and are emerged as a convenient way of dosing medications, not only to special population/groups with swallowing difficulties such as children and the elderly, but also to normal people. MDF are prepared using hydrophilic polymers that rapidly dissolve on the tongue or in the buccal cavity, delivering the drug to the systemic circulation via dissolution on contact with saliva. MDF are typically designed for oral administration, with the user placing the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal). As the strip dissolves, the drug can enter the blood stream primarily buccally and sublingually[10].

Owing to large surface area of the film formulation, there is greater disintegration and dissolution in the oral cavity. As the drug is absorbed through buccal mucosa, first pass metabolism is avoided thus enhancing the bioavailability. Films prove to be advantageous in case of dysphagic patient. As compared to orally disintegrating tablets the films are less fragile and hence provide ease of transportation[11]. Nowadays, Mouth dissolving films are also prepared by using natural excipients and it is found to be very much effective as compared to normal excipients. Natural polysaccharide extracted from tubers of *Colocassia esculenta* (also known as taro gum) has been used a polymer for film formulation along with semisynthetic polymer HPMC (Hydroxy propyl methyl cellulose)[12]. Also, the films using established natural polymers namely xanthan gum, guar gum, gum ghati and sodium alginate are formulated in combination with HPMC. The natural polymers are comparatively cheaper with desired properties like abundantly available, non-irritating and non-toxic in nature[13].

ADVANTAGES OF MOUTH DISSOLVING FILMS (MDFs)

The administration of MDFs has numerous advantages and some of them are as follows:

- Easy transportation.
- Ease of swallowing for geriatrics and pediatrics.
- Convenient and accurate dosing.
- No requirement of water for administration.

- Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.
- Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability[7].

DISADVANTAGES

- Dose uniformity is a technical challenge.
- Hygroscopic in nature.
- High doses cannot be incorporated (<40 mg/4cm2 piece)
- Require special packaging for products stability and safety[7].

SPECIAL CHARACTERISTICS OF MOUTH DISSOLVING FILMS

- Thin elegant film
- Unconstructive
- Available in various size and shapes
- Fast disintegration
- Rapid release
- Give a pleasant mouth feel.
- Have an acceptable taste.
- Should not leave residues in mouth[7].

FORMULATION ASPECTS FOR MOUTH DISSOLVING FILMS:

Active Pharmaceutical Ingredient:

Various classes of drugs can be incorporated into MDFs e.g., anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc. Dimenhydrinate can also be incorporated into MDFs for taste masking. Common examples of drugs incorporated into MDFs are salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine**,** tianeptine sodium, indomethacin, etc[7].

Film Forming Polymer:

Water-soluble polymers are used as film formers as they provide quick disintegration, good mouth feel, and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations. A variety of polymers are available for preparation of films of which pullulan, gelatin and hypromellose are most commonly used. Examples of water-soluble polymers include: Pullulan, Gelatin, guar gum, xanthan gum, Hydroxyl propyl methyl cellulose (HPMC), Modified starches, PVPK30, PVA etc. HPMC E3/E5/E6/E15.

Ideal properties of the polymers used in the oral film:

- Polymers should be nontoxic, non-irritant and non-bitter.
- Polymers should be tasteless.
- It should be devoid of leachable impurities.
- It should be inexpensive and readily available[14,15].

Sweetening Agent:

Sweeteners have become an important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations.

Some suitable sweeteners include:

- Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc.
- Water soluble artificial sweetener: sodium or calcium saccharin salts, acesulfame-K etc.
- Dipeptide based sweetener: aspartame

Saliva Stimulating Agent:

Salivary stimulants are generally acidic in nature stimulating the production of saliva in buccal cavity, consequently, promoting the disintegrating of MDFs. Some commonly used saliva stimulating agents are citric acid, maleic acid, tartaric acid, ascorbic acid and lactic acid.

Surfactant:

Surfactants are used as solubilizing or wetting or dispersing agents as a result that

the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal films. E.g.: Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, tweens and spans etc.

Flavor:

Flavors are needed to mask the bitter or nauseating taste of incorporated drug. Amount of flavor depends upon its nature and strength. Any US-FDA approved flavor can be used such as sweet, sour or mint flavor one of the research work verified that mint, liquorice and sucralose mixture flavors appropriately mask the bitter taste of diclofenac sodium. Electronic tongues are used to discriminate the effect of various taste masking agents (TMAs).

Colouring Agent:

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1% w/w) in oral strips when some of the formulation ingredients or drugs are present in insoluble or suspension form[16].

Natural Excipients:

Natural excipients are preferred on the synthetic and semisynthetic ones because of their lack of toxicity, low cost, soothing action, availability, and nonirritant nature of the excipients[17].

Because of cost efficacy and regulatory acceptance natural gums are the most popular hydrophilic polymers[18,19,20].

Advantages of Natural Polymers

- As the name indicates they are available in nature so that they are biodegradable in nature, and they are produced by all living organisms.
- All of these plant materials are reiterating sugar polysaccharides these are biocompatible and non- toxic.
- When compared to synthetic materials cost of production is less for natural polymers.
- Large quantities of natural polymers are produced due to simple production processes are involved.
- Minimum chance of adverse and side effects with natural polymers when compared with synthetic materials.
- There is promotion being done by government for the plant production as pharmaceutical excipients, and it withal provides the facilities for bulk production, because of their wide applications like gum and mucilage's in industries in India and homogeneous developing countries.

Natural polymers are various plant-based materials. Plant-based material serves as an alternative to synthetic products because of different reasons:

- Ecological in nature.
- Bio-acceptability.
- Having renewable source as well as lowest price when compared to synthetic products.

Guar gum

It is also called guaran, is a galactomannan with high molecular weight of 8,000,000. It is obtained from the Guar plant as an endosperm seed Cyamopsis tetragonoloba (L) Taub. (Synthetic Cyamopsis psoralioides). It is free flowing, consummately soluble, neutral polymer which is composed of sugar units and has also been approved for use in food. Guar gum and derivatives are used as binders and disintegrate in films and also used as a controlled- released agent for the drug. It is used in a concentration of 1% w/w as a disintegrant for the preparation of oral films.

Mangifera indica gum (MIG)

In various pharmaceutical formulations MIG is used as a disintegrating agent, binder, suspending agent, and emulsifying agent because of its non-toxic nature. It is

used as a polymer in formulation of oral films.

Dehydrated banana Powder (DBP)

Additionally, banana is called as plantain. DBP is used as a superdisintegrant in the formulation of oral films. It is a very good source of energy due to high carbohydrate content, and it contains potassium, which is responsible for more preponderant brain functioning.

Pullulan

Pullulan is a natural and extracellular microbial polysaccharide produced by the fungus-like yeast, Aureobasidium pullulans. Pullulan can be made into very thin films (down to 0.01mm) which also have more tensile strength and can stable over a range of temperatures. Pullulan can be made into films of high tensile strength and low oxygen permeability, are oil and grease resistant. Pullulan films are usually prepared with 5-10% aqueous pullulan solution by rapid evaporation and applied to a smooth surface and dried; it may also involve the use of high temperature and pressure. Pullulan can be mixed with gelatin, amylose and polyvinyl alcohol for better release of drug.

Plasticizers

Plasticizers are the additives that increase the plasticity or fluidity of a material. Plasticizer mainly reduces the brittleness of the strip and imparts flexibility. Based on the compatibility with the polymer, plasticizer should be selected and also based on the type of solvent used for casting of the strip commonly used plasticizers in the formulation of oral films are in the concentration of 0-20% w/w of dry polymer weight.

- Glycerol
- Propylene glycol
- Castor oil
- Polyethylene glycols with low molecular weight
- Tributyl citrates, Triethyl citrates, Actyl citrates

In comparison to citric acid, tartaric acid and oleic acid Maleic acid was found to be better plasticizer as it did not crystallize out after drying of the films. Maltodextrin can also be plasticized as and converted with incorporation of glycerine as well as propylene glycol as plasticizer into oral dissolving film in the concentration range of 16-20% w/w, and found to be more advantageous by using glycerin over propylene glycol as it shows miscibility problems with maltodextrin either by using hot melt extrusion or solvent casting methods[21,22,23,23,24].

METHODS OF PREPARATION OF MOUTH DISSOLVING FILM:

One or a combination of the following processes can be used to manufacture the Mouth dissolving film:

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

1. Solvent Casting Method:

Solvent casting is the most commonly used method for the preparation of MDFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor. Then, the prepared solution is poured onto petri plate and the solvent is allowed to dry by exposing it to high temperature in order to attain good quality films. In solvent casting technique, film forming polymer is usually soaked in an appropriate solvent for overnight. The type of API, which has to be incorporated in MDF, governs the selection of a suitable solvent depending on critical physicochemical properties of API such as melting point, shear sensitivity and polymorphic form. Compatibility of drug with solvent and other excipients is also brought under consideration before finalizing a formulation. During formulation, entrapment of air bubbles can hinder the

uniformity of prepared films. Thus, deaeration of the mixture is carried out with the help of a vacuum pump. Viscosity of the solution to be poured is an imperative aspect in casting method. The concentration of pullulan varying from 2% to 8% results into low viscosity solution, as a result, enabling easy casting of films[2,25,26].

2. 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.

3. Semi Solid Casting Method:

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. Acid insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

Solution of water-soluble film forming polymer is prepared. Then resulting solution is added to a solution of acid insoluble polymer. After that appropriate amount of plasticizer is added so that gels mass is obtained. Finally, the gel mass is casted into the film or ribbons using heat controlled drums.

4. Solid Dispersion Extrusion Method:

Solid dispersion of domperidone using beta-cyclodextrin, PEG400 and HPMC E15 was successfully prepared and films were casted using solid dispersion extrusion method[2,27,28]].

5. Rolling Method:

In rolling method, a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water or a mixture of water and alcohol. The film is dried on the rollers and cut into desired shapes and sizes.

EVALUATION PARAMETERS:

Thickness test:

Thickness of a film is determined by using calibrated digital micrometer and then subsequently mean average is calculated. Generally, three readings from all the batches are determined and average is calculated.

Weight variation:

Weight variation of a film is calculated in triplicate by cutting the film and determining weight of each film. Uniformity in weight is important to ascertain as it is directly proportional to dose accuracy of the film.

Tack test:

Tack is the tenacity with which the film adheres to the accessory that has been pressed into contact with strip. This test also determines the dryness.

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:

$$\text{Tensile strength} = \frac{\text{Load at breakage}}{\text{Strip thicknss}} \text{ x Strip width}$$

Percentage elongation:

When the sample films are subjected to tensile stress, deformation of the films occurs resulting in stretching or elongation of sample. It is performed to predict the

ductility of polymers using a texture analyzer. It is calculated by formula:

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original length}} \text{ x } 100$$

Folding endurance:

To determine folding endurance, a portion of film is cut and repeatedly folded at the same point till it breaks. The number of times the film could be folded at the same point without breaking indicates the folding endurance value. Typical folding endurance for a film range between 100-150.

Swelling property:

Simulated saliva solution is used to check the swelling studies of films. Initial weight of film is determined and is placed in pre weighed stainless steel wire mesh. This mesh containing film is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant pre-determined time intervals until no more increase in weight. Degree of swelling is determined by these parameters:

$$\text{Degree of swelling} = \frac{\text{Final weight } (W_t) - \text{ Initial weight } (W_0)}{\text{Initial weight } (W_0)} \text{ x } 100$$

W_t = weight of film at time interval t, W_0 =weight of film at time 0.

Surface pH:

The pH value of a film is usually determined by putting the prepared film in petri dish and subsequently film is made wet by using distilled water and noting pH by touching the film surface with a pH meter electrode. Determination of surface pH is vital as acidic or basic pH is liable to cause oral mucosal irritation.

Content uniformity:

Contents of a film are determined by standard assay method specified for individual drug in different Pharmacopoeia. This test is performed on 20 samples using analytical techniques. The acceptance value of the test is less than 15% in accordance with Japanese Pharmacopoeia. According to USP27, the contents should range from 85% to 115% with the standard deviation of less than or equal to 6% content uniformity is worked out for estimating drug contents in individual film.

Disintegration time:

Disintegration apparatus mentioned in official Pharmacopoeias is used for determining the disintegration time of a film. Normally, the disintegration time is the function of composition of film as it varies with the formulation and generally ranges from 5 to 30 s. Mostly, the USP disintegration apparatus is used for this test. There are no official guidelines available for determining disintegration time of orally fast disintegrating films. There are two methods for determining disintegration time of film.

Slide frame method: A drop of distilled water is poured onto the film clamped into slide frames placed on petri dish. Time taken by the film to dissolves noted.

Petri dish method: A film is placed into 2 ml distilled water taken in Petri dish. Time taken by the film to dissolve completely is considered as the disintegration time.

In-vitro dissolution test: Standard official basket or paddle apparatus is used for conducting dissolution studies on films. Sink conditions should be maintained

during dissolution. Sometimes while performing this process, film floats over the medium making it difficult to perform the test properly. This problem is more likely to occur in case of paddle method, thus the basket apparatus is mostly preferred. Media used are phosphate buffer pH 6.8 (300 ml) and 0.1 N HCl (900 ml). Temperature is maintained at 37 ± 0.5^0C and rotation speed of 50 rpm is usually adjusted. Samples of drug dissolved are collected at pre-determined intervals and are analyzed by using UV-spectrophotometer. Despite its extensive use, dissolution test is still prone to noteworthy inaccuracy and tests let down[2].

CONCLUSION:

The present review shows that mouth dissolving films are one of the novel approaches in the field of pharmaceutical sciences. They have improved acceptance and patient compliance with no risk of choking associated with better safety and efficacy in comparison with conventional dosage forms. The main idea behind formulation of MDFs was to manage with the difficulty in swallowing conventional oral dosage forms among pediatric, geriatric and psychiatric patients with dysphagia. Presently, MDFs are widely available for hypertension, acidity, allergy, pain, etc. reflecting their importance. Major advantages of such dosage form are their administration without the use of water fulfilling the need of target population seeking convenience in drug administration along with bypassing the hepatic metabolism, consequently, leading to improved therapeutic response.

Because of their rapid disintegration, improved dissolution properties principally with paediatric and geriatric patients, oral fast dissolving films are considered as most promising and important drug delivery systems. Use of Natural excipients in the preparation of mouth dissolving films is preferable due to advantage of being less expensive, biodegradable, and ecofriendly nature as compared to synthetic excipients.

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