EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 4
158-163
Year: 2019

MOUTH DISSOLVING FILMS: AN EFFECTIVE ORAL DISINTEGRATING DRUG DELIVERY SYSTEM

Venkateswara Rao S.[1]*, Bhavya G.[1] and Padmalatha K.[2]

Department of Pharmaceutics[1], Department of Pharmacology[2],
Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada–521108, India.

***Corresponding Author: Prof. Venkateswara Rao S.**
Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada–521108, India.

Article Received on 07/02/2019 **Article Revised on 27/02/2019** **Article Accepted on 21/03/2019**

ABSTRACT
The drug discovery and development of new chemical entity is not only an expensive but also time consuming affair. Hence the pharmaceutical industries are focusing on designing and development of innovative drug delivery systems for the existing drugs. One of such delivery systems is mouth dissolving film, which has gained the popularity among the pediatric and geriatric patients. This mouth dissolving film with many potential benefits of a fast disintegrating tablet but devoid of friability and risk of choking is more acceptable to pediatric and geriatric patients. In view of the advantages of the mouth dissolving films over the fast disintegrating tablets and other dosage forms, it has the potential for commercial exploitation. Formulation of mouth dissolving film can be achieved by various techniques, but the common methods of preparation include spraying and casting. These techniques use hydrophilic film former in combination with suitable excipients, which allow the film to disintegrate or dissolve quickly in the mouth within a few seconds without the administration of water. The oral disintegrating films not only have certain advantages of other fast disintegrating systems but also satisfy the unmet needs of the market. The present review focuses on benefits, formulation development, characterization and applications of orally fast disintegrating films.

KEYWORDS: Oral disintegrating films, Casting method and Hydrophilic film former.

INTRODUCTION
Oral drug delivery systems still need some advancement to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets.[1] The most common complaint was tablet size, followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water.[2] So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water.[3] Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention.[4]

Orally fast-dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, 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 oromucosal and intragastric absorption.[5] Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of $500 million in 2007 and could reach $2 billion in 2012. Based on upward global growth trends of the past decade, the fast dissolving dosage market could produce revenues of $13 billion by 2015.[6]

Special features of mouth dissolving films

1. Thin elegant film
2. Available in various size and shapes
3. Unobstructive
4. Excellent mucoadhesion
5. Fast disintegration
6. Rapid release

The ideal characteristics of a drug to be selected

1. The drug should have pleasant taste.
2. The drug to be incorporated should have low dose upto 40 mg.
3. The drugs with smaller and moderate molecular weight are preferable.
4. The drug should have good stability and solubility in water as well as in saliva.
5. It should be partially unionized at the pH of oral cavity.
6. It should have the ability to permeate oral mucosal tissue

Advantage of mouth dissolving films

1. Mouth dissolving films can be administered without water, anywhere, any time.
2. Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
3. Mouth dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
4. Suitability for geriatric and pediatric patients, who experience difficulties in swallowing mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.
5. Beneficial in cases such as motion sickness, acute pain, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.
6. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
7. As compared liquid formulations, precision in the administered dose is ensured from each strip of the film.
8. The oral or buccal mucosa being highly vascularized, drugs can be 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.[7]
9. 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 the medicament.[8]

Disadvantages of mouth dissolving films

1. High doses cannot be incorporated.
2. Dose uniformity is a technical challenge

Table-1: Comparison between orally fast dissolving films and tablet.

Orally Dissolving Films	Oral Disintegrating Tablets
It is a film	It is a tablet
Greater dissolution due to larger surface area	Lesser dissolution due to less surface area
Better durable than oral disintegrating tablets	Less durable as compared with oral films
More patient compliance	Less patient compliance than films
Low dose can only be incorporated	High dose can be incorporated
No risk of chocking	It has a fear of chocking

FORMULATION CONSIDERATION

Active pharmaceutical ingredient

A typical composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in MDFs. Multi vitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and also for better dissolution and uniformity in the MDFs.[9]

Many APIs, which are potential candidates for MDF technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the MDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste. This is often termed as obscuration technique.

Table-2: Mouth dissolving films are of Some Drugs.

Drug	Action	Dose (mg)
Salbutamol	Anti asthmatic	4
Levocetrizine	Anti asthmatic	75
Chlorohexidine	Antiseptic	12
Ondensteron	Antiemetic	2.5

Film forming polymer

Since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity, the final film that is used must necessarily be water soluble. In order to prepare a thin film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity. The polymer employed should be non-toxic, non-irritant and devoid of leachable impurities. It should have good wetting and spread ability property. The polymer should exhibit sufficient peel, shear and tensile strengths. The polymer should be readily available and should not be very expensive. Many different polymers for use in oral films are proposed in the literature, and various research groups have introduced different materials.[10] The polymers can be used alone or in combination to improve hydrophilicity, flexibility, mouth feel and solubility characteristics of fast dissolving films. The stiffness of the strip depends on the type of polymerand the amount of polymer in the formulation. Polyvinyl pyrrolidone films are brittle in nature and therefore copovidone is mixed with poly vinyl pyrrolidone for preparation of flexible fast disintegrating films. Combination of microcrystalline cellulose and maltodextrin has been used to formulate fast dissolving films of piroxicam made by hot melt extrusion technique. In this case, microcrystalline cellulose is used to render the film non-sticky and smooth. Microcrystalline cellulose was also used to decrease the disintegration time and improve the dissolution of drug from the films. Watersoluble polymer that may be used include natural gums such as those derived from guar, xanthun, acacia, Arabicor tragacanth, other available polymers are, polyethyleneoxide, acrylic based polymer and several types of sodiumcarboxymethyl cellulose (CMC), several types of hydroxypropyl methyl cellulose (HPMC), a synthetic copolymer of polyethylene glycol–polyvinyl alcohol (Kollicoat IR) and sodium alginate. Cellulose ethers are widely available and economical. Pullulan, an a-1,6-linked maltotriose produced from the fungus Aureobasidiumpullulans, has also been used. Five starches and maltodextrin have also been investigated as alternative film formers. The physicochemical characteristic of the polymer or polymers selected for film formulation play a vital role in determining the resultant disintegration time of the cast thin film oral dosage form.

Plasticizer

Plasticizer is a vital ingredient of the fast dissolving films. Plasticizer helps to improve the flexibility of the strip and reduces the brittleness of the films. It significantly improves the film forming properties by reducing the glass transition temperature of the polymer. The chemical structure and concentration of plasticizers play an important role in alleviating the glass transition temperature of the polymers. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of film. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such astributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20 percent; w/w of dry polymer weight. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.[11]

Table No-3.

GLYCEROL	PROPYLENE GLYCOL
Polyethylene glycols	Phthalate like dimethyl, diethyl, dibutyl derivatives
Citrate derivatives	Castor oil

Sweetening agents

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. Both natural sweeteners as well as artificial sweeteners are used in the formulation of these fast dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Aspartame was used for the preparation of oral strips of valdecoxib. Sucralose and neotame was reported to be used in the suppression of the bitter taste of fast dissolving films of diclofenac and ondansetron respectively.[10]

Saliva stimulating agent

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 rapid dissolving strip formulations. Generally acids which are used in the

preparation of food can be utilized as salivary stimulants.[11]

Eg. Citric acid, malic acid, lactic acid, ascorbicacid and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.

Flavoring agents

Preferably up to 10%w/w flavors are added in these formulations.[12] The acceptance of the oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The selection of flavor is dependent on the type of drug to be incorporated in the formulation. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. Flavoring agents can be selected from 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. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type.[13]

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.

METHOD OF PREPARATION

Following process can be used combinly to manufacture the mouth dissolving films.

Solvent casting method

In solvent casting method excipients are dissolved in water, then water soluble polymers and in last drug is added and stirred to form homogeneous solution. Finally solution is casted in to the Petri plate and dried.[14]

Semisolid casting

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. In Semisolid casting method gel mass is casted in to the films or ribbons using heat controlled drums. Gel mass is obtained by adding solution of film forming to a solution of acid insoluble polymer in ammonium or sodium hydroxide. 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.[15]

Hot melt extrusion

In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then dried granular material is introduced into the extruder. The screw speed should set at 15 rpm in order to process the granules inside the barrel of the extruder for approximately 3 - 4 min. The processing temperatures should be 80^0C (zone 1), 115^0C (zone 2), 100^0C (zone 3) and 65^0C (zone 4). The extrudate (T = 65^0C) then pressed into a cylindrical calendar in order to obtain a film.[16] There are certain benefits of hot melt extrusion include fewer operation units, better content uniformity and an anhydrous process.

Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.[17]

Rolling Method

In rolling method a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol.[16] The film is dried on the rollers and cutted in to desired shapes and sizes.

CHARACTERIZATION OF MDFS

The fast disintegrating oral films are evaluated for the following parameters.

Visual Inspection: Oral fast dissolving films were inspected manually for their transparency and air bubble.

Thickness measurement: Thickness of the film is measured by using a dial gauge tester. Thickness at different points is measured from which the average thickness of the FDOF is determined.[13]

Measurement of folding endurance: In order to carry out the endurance study, the strip of film is repeatedly folded at the same place until it breaks. The number of time the film is folded at the same place prior to breaking gives the folding endurance.

pH: pH measurement is carried out by keeping the film in contact with distilled water, and after 1 hour, the pH of the solution or dispersion is measured.

Moisture uptake: The test is done by keeping previously weighed film in desiccators at a particular temperature and relative humidity. After three days, the film is taken out and reweighed to determine the percentage of moisture uptake.[18] Percentage of moisture uptake can be calculated as follows.

$$\% \text{ Moisture Uptake} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Initial Weight}} \times 100$$

Moisture content: Previously weighed films are stored in a desiccator for 24 hours. The final weight is noted when there is no further change in the weight of

individual film. Percentage of moisture content, can be calculated as follows,

$$\% \text{ Moisture Uptake} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Disintegration time: It is the time at which the film begins to break when brought into contact with water. It can be determined by keeping a film of desired size in a Petri dish containing water and noting the time it takes to break.

Dissolution time: It is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media. It can be done by both in vitro and in vivo methods. In vitro dissolution time can be determined by keeping a desired piece of film in Petri dish containing water and noting the time required to dissolve at least 80% of the film. In vivo dissolving time of film is studied by selecting different aged group of volunteer. The films of desired size should be kept in their oral cavity till they completely dissolve without any residue left in mouth and in vivo dissolving time of film is noted.[19]

APPLICATIONS

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 applications.

Oral mucosal delivery via Buccal, sublingual, and mucosal route by use of OTFs could become a preferential delivery method for therapies in which rapid absorption is desired, including those used to manage pain, allergies, sleep difficulties, and central nervous system disorders.[20]

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.[21]

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.

STORAGE AND PACKAGING

A variety of packaging options are available for fast dissolving films. The rolled film can be die-cut into any shape or size or slit into narrower rolls as required for the application. Single packaging is mandatory for films, which are pharmaceutical products; an aluminum pouch is the most commonly used packaging format. APR-Labtec has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually. For branding purposes and to meet industry regulations, converters may choose to print information directly onto the film unit doses before packaging.

MARKETED PRODUCTS OF ORAL STRIPS

Product category	Ingredient/s	Applications
Appetite suppressant	Fucus vesiculosus, guarana extract and garcinia cambogia	These are top selling natural ingredients associated with weight loss.
Vitamins and food supplements	Various vitamins, minerals and supplements	It is useful for the people who do not like to pop up the tablets
Breath freshener strip	Contain mint flavor and antibacterial agent and cetylpyridinium chloride	It is used as mouth freshener and to stop bad breath
Saliva promoting strips	Fruit acid extracts, range of flavors	It is used in the dry mouth as a side effect of the other medications.
Ondansetron Rapid film	Ondansetron 4 mg and 8 mg.	It is used in the prevention of chemotherapy and radiation- induced nausea and vomiting and prevention of postoperative nausea and vomiting
Donezepil Rapidfilm	Donepezil Hydrochloride 5 mg and 10 mg.	Treatment of mild to moderately severe dementia of the Alzheimer's type
Minerals	Chromium	Mineral supplements
Natural products	Ginseng, Guarana	Aphrodisiac, Appetite reducer
Innozen Inc Chloraseptic Relief Strips™	Benzocaine, Hydroxypropyl methylcellulose, malicacid, menthol, monoammonium glycyrrhizinate, cherry flavors, polyethylene oxide, sucralose	Occasional minor irritation, pain, sore throat and sore mouth
Loratidine	Loratidine 10 mg-20 mg	It is a non sedative antihistaminic agent used to treat the allergy

CONCLUSION

The present review shows that mouth dissolving films are one of the novel approaches in the field of pharmaceutical sciences. The mouth dissolving film a new dosage forms for all age groups, specifically pediatric, geriatric patients and patients with swallowing difficulties. 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.

ACKNOWLEDGMENTS

The presenting authors are thankful to principal, Vijaya institute of pharmaceutical sciences for women, Vijayawada for their valuable support in carrying out this work.

REFERENCES

1. Joseph F Standing, Catherine Tuleu. Paediatric formulations—Getting to the heart of the problem. International Journal of Pharmaceutics, 2005; 300: 56–66.
2. Habib W, Pritchard JF, Bozigian HP, Gooding AE, Griffin RH, Mitchell R, Bjurstrom T, Panella TL, Huang AT, Hansen LA. Fast-dissolve drug delivery system. Crit. Rev. Ther. Drug Carrier Syst., 2000; 17: 61–7.
3. Anderson O, Zweidorff OK, Hjelde T, Rodland EA. Problems when swallowing tablets. Tidsskr NorLaegeforen, 1995; 115: 947-949.
4. Liang C A, Chen HL. Fast dissolving intraoral drug delivery systems. Expert Opin. Ther. Patents., 2001; 11: 981-986.
5. Patel RA, Prajapati SD. Fast dissolving films as a newer venture in fast dissolving dosage forms. International Journal Drug Development & Research, 2010; 2(2): 232-246.
6. Technology catalysts International Corporation, accessed on 2011 feb 14th Available from http://www.technologycatalysts. Com
7. Mashru RC, Sutariya BC, Parikh PP. Development and evaluation of fast dissolving films of salbutamol sulphate. Drug Dev Ind Pharm., 2005; 31: 25-34.
8. Gohel MC, Sharma R, Soniwala MM. Development of taste masked film of Valdecoxib for oral use. Indian Journal of Pharmaceutical Sciences, 2007; 69: 318-320.
9. Koland M, Charyulu N. Fast dissolving sublingual films of ondansetron hydrochloride: Effect of addivites on *invitro* drug release and mucousal permeation. Journal of Young Pharm, 2010; 2: 216-221.
10. Kulkarni AS, Deokule HA. Exploration of different polymers for use in the formulation of oral fast dissolving strips. Journal of Current Pharm. Res., 2010; 2: 33-35.
11. Singh S, Gangwar S. Formulation and evaluation of rapidly disintegrating film of levocetrizine hydrochloride. Der Pharmacia Lettre., 2010; 2: 434-439.
12. Juliano C, Cossu M. Preparation, In Vitro Characterization and Preliminary *In Vivo* Evaluation of Buccal Polymeric Films Containing Chlorhexidine. AAPS Pharm Sci Tech., 2008; 9: 1153-1159.
13. Gavaskar Basani, Kumar Subash Vijaya, Guru Sharan, Rao Y Madhusudan. Overview on fast dissolving films. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(3): 29 - 33.
14. M Nishimura, K Matsuura, T Tsukioka, H Yamashita, N Inagaki, T Sugiyama, Y Itoh. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. International Journal of Pharmaceutical Scienses, 2009; 368(2): 98–102.
15. Shimoda H, Taniguchi K. Preparation of fast dissolving or thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. European Journal of Pharmaceutics and Biopharmaceutics, 2009; 73: 361-365.
16. Arya A, Chandra A. Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form. International Journal of Chem Tech Research, 2010; 2: 576-583.
17. Cilruzo F, Cupone EI. Fast dissolving films made of maltodextrins. European Journal of Pharmaceutics and Biopharmaceutics, 2008; 70: 895-900.
18. Khurana R, Alka A and Khar RK. Development and Evaluation of Mucoadhesive Films of Miconazole Nitrate. Indian J Pharm Sci., 2000; 6: 448-452.
19. Vishwkarma DK, Tripathi AK, Yogesh P and Maddheshiya B. Review article on mouth disintegrating film. J Global Pharma Tech., 2011; 3(1): 1-8.
20. Barnhart SD, Sloboda MS. The future of dissolvable films. Drug Del Technol, 2007; 7(8): 34-37.
21. Meathrel B, Moritz C. Dissolvable films and their potential in IVDs. IVD Technol, 2007; 13(9): 53-58.