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AN EMERGING CONCEPT IN ORAL DRUG DELIVERY SYSTEM: MOUTH DISSOLVING SUBLINGUAL FILMS

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ABSTRACT

Sublingual route is a very useful for rapid onset of action with better patient compliance. It provides better drug utilization and improves the efficacy of active pharmaceutical ingredients.The tablet and capsules are most popular oral solid dosage form.Many patients are difficult to swallow capsule and tablet mostly for pediatric and geriatric patients.In some cases such as sudden episode of allergic attack, motion sickness, fear of choking and an unavailability of water the swallowing of tablet and capsule is difficult. To overcome these difficulties, fast dissolving sublingual film is developed. It improves the efficacy of API's and provides better drug utilization. The sublingual route of drug administration is very effective since the drug absorbed through the sublingual blood vessels by passes hepatic first pass metabolic process and gives a better bioavailability. The present article overviews the formulation aspects, manufacturing methods like solvent casting, evaluation parameters and applications of fast dissolving films by sublingual route.

KEYWORDS: Fast dissolving films, Mouth dissolving films, Self-micro-emulsifying mouth dissolving film and Application, Sublingual films.

INTRODUCTION

Oral fast dissolving film (FDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self-administration without water or chewing. The need for non-invasive delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management. Approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. Most of the existing fast-dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth within a few seconds or minutes, without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. The film overcome the danger/fear of choking. The development of a fast-dissolving sublingual film also provides an opportunity for a line extension in the market place; a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, anti-asthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form.[1,2-6] 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.[7,8]

Concept of oral dissolving film

- 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.
- This delivery system consists of a thin film.
- No need of water has led to better satisfactoriness amongst the dysphasic patients and to better acceptance during travelling without carrying water.
- 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]

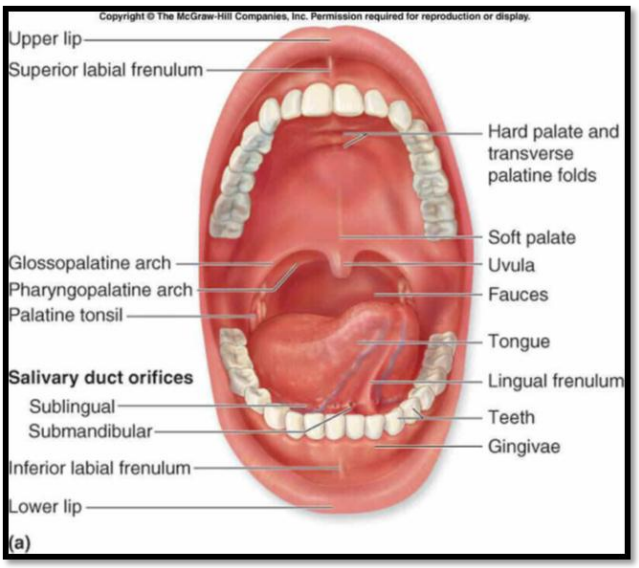

Fig (1): Overview of Oral mucosa.

Special features of mouth dissolving films

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Fast disintegration
- Rapid release
- Excellent mucoadhesion

Ideal characteristics of a drug

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

Table1: Comparison between orally fast dissolving film and oral disintegrating tablets.

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

Classification of Oral Film

There are three different types of oral films

1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained-release wafers

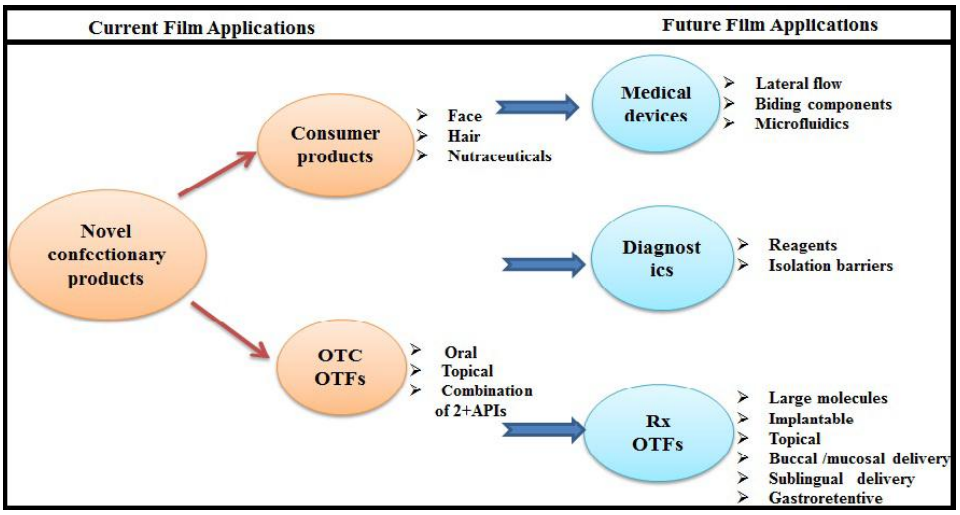

Fig (2): Evaluation of dissolvable films "OTC OTFs" are over the counter oral films "APIs" are active pharmaceutical ingredients.

Formulation Consideration

- Active pharmaceutical ingredient
- Film forming polymers
- Plasticizer
- Sweetening agent
- Saliva stimulating agent
- Flavoring agent
- Coloring agent

Table 2: Composition of fast dissolving oral film.

Sr. No	Composition of Film	Quantity
1	Active pharmaceutical agent	1-25%
2	Film forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Flavoring agent	10%
7	Coloring agent	1%

1. Active pharmaceutical agent

The drugs selected for oral films should possess good stability in saliva and water with low dose. The film should consist of 1-25% w/w of the drug. Small dose molecules are the best candidates to be incorporated in Oral fast dissolving film. Multi vitamin sup to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60seconds. 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 Oral fast dissolving film.

2. Film forming polymer

A variety of polymers are available for preparation of fast dissolving films. The polymers can be used alone or in combination to obtain the desired films properties. The films obtained should be tough enough so that there won't be any damage while handling or during transportation.[10]

The polymers can be used alone or in combination to obtain the desired strip properties. Water-soluble polymers are used as film formers. The use of film forming polymers in dissolvable films has attracted considerable attention in medical and nutraceutical application. 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 base. Both natural as well as synthetic polymers can be used in the formulation of sublingual films. In order to prepare a film formulation that is water-soluble, excipients or polymer must be water soluble with low molecular weight and excellent film forming capacity.[11]

Table 3: List of Film forming polymers.

S. No	Polymer Used
1	HPMC E – 15 + PEG 400
2	HPMC E – 15 + GLYCERIN
3	HPMC E – 15 + MCC
4	Hydroxypropyl cellulose
5	Corn starch
6	GUAR GUM
7	XANTHUN GUM

3. Plasticizers

Plasticizers are the essential additives that are able to change hard and brittle films to more pliable and tougher form. Plasticizer is usually low molecular weight organic solvent, having

Tg values of -50oC to -150oC. Most of the polymers used in film coating are either amorphous or have very little crystallinity. Most commonly employed plasticizers are glycerol, propylene glycol, sorbitol, and/or polyethylene glycol. The plasticizer may be present in any desired amount, particularly from 0 to about 50 percent, more typically from 5 to about 20 by weight of the active containing formulated film.[12]

Plasticizer molecules interpose themselves between the individual polymer strands; thus, break-down polymer-polymer interactions to a large extent. This action is facilitated as the polymer plasticizer interaction is considered to be stronger than the polymer-polymer interaction thus providing greater opportunity to polymer strands to move past each other. The interaction of the plasticizer with the polymer generally decreases the elastic modulus, lowers the softening temperature, and decreases the Tg[13] Glycerol, propylene glycol, low molecular weight propylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0-20% w/w of the dry polymer weight. Honary et al. studied effect of different molecular weights and concentration of PEG as plasticizer in HPMC film.

4. 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. E.g. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.[14]

5. Flavoring agents

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 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.[14]

6. 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. E.g. Titanium dioxide.

METHOD OF PREPARATION OF SUBLINGUAL FILMS

Various approaches to manufacturing of rapid dissolving film are classified as follow:

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

Solvent casting

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.[15,16]

Semisolid casting

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.

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 800C (zone 1), 1150C (zone 2), 1000C (zone 3) and 650C (zone 4). The extrude (T = 650C) then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion.[17,18]

- Fewer operation units
- Better content uniformity
- 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.

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. The film is dried on the rollers and cutted in to desired shapes and sizes.[17]

Application of Oral Strip in Drug

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 applications.

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.[19] 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 devices.[20]

Self-micro-emulsifying mouth dissolving film (SMMDF)

A self-micro-emulsifying mouth dissolving film (SMMDF) is a dosage form which is based on mouth dissolving film integrated with self-micro emulsifying components. Stability of self-micro emulsifying drug delivery system is one of major problem of lipid based drug delivery system. This can be minimized by converting liquid self-micro emulsifying drug delivery system into solid SMMDF. This drug delivery system enjoys both advantages of self-micro emulsifying drug delivery system (SMEDDS) along with mouth dissolving film (MDF). Self-micro-emulsifying mouth dissolving film formulations can be used to improve the oral bioavailability of hydrophobic drugs due to their efficiency of presenting the

hydrophobic drug in solubilized form. Self-emulsifying mouth dissolving film is promising approach for the formulation of drugs with poor aqueous solubility, high molecular weight, pre-systemic first pass effect, enzymatic degradation, gastric irritation, limited dissolution rate and low bioavailability. SMMDF is used to improve dissolution characteristics of a poorly water soluble drug as it maintains the drug in a solubilized form and has quick onset of action. Solid-SMEDDS is also a solid dosage form but it cannot avoid first pass metabolism of drug. SMMDF is economic as it requires less quantity of drug and less complicated machineries. SMMDF appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophilic drugs. This study explores the possibilities of loading a wide variety of plant actives as their scale up is convenient and economical.

CONCLUSION

MDFs are convenient and reliable dosage forms that can circumvent problems associated with solid dosage forms. The commercial launch of MDFs was primarily in OTC, but now their use has been extended to prescription drugs. MDF are preferred to MDT which requires expensive manufacturing, special packaging due to their fragile nature. MDFs are not well defined in the literature but, no doubt a revolutionary and an innovative drug delivery system for all the population groups, specifically geriatric, pediatric patients and patients with swallowing difficulties. This technology is growing fast pace challenging most of the pharmaceutical companies to develop oral films for a wide range of active pharmaceuticals ingredients.

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