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FAST DISSOLVING ORAL FILMS: A NOVEL TREND IN DOSAGE FORM

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Abstract:

Oral routes are most commonly preferred route for drug delivery. Commonly used oral dosage forms are tablet and capsules. But many patients such as geriatric, paediatric and dysphasic patients find difficulty in swallowing conventional tablet and capsule. To overcome the problems related to swallowing, Fast dissolving Tablets (FDTs) were designed in early 19th century and hence further advancement has led to development of Fast Dissolving Oral Films (FDOFs). Many pharmaceutical groups are focusing their research on rapid dissolving technology. FDOFs technology is gaining much attention. This technology has been used for local action as well as rapid release products. The fast dissolving oral films may compose of various Active pharmaceutical ingredients (API), film forming polymers, plasticizer, flavours, colours and sweeteners. Now a day, such types of films became a novel and widely accepted technology for delivering OTC and prescription medication too.

Keywords: *Introduction, Advantages, Disadvantages, Formulation Ingredients, Method Of Preparation, Patented Technologies.*

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INTRODUCTION:

The oral route is the perfect route for the administration of therapeutic agents. This route has low cost of therapy, accurate dose, self- medication, pain avoidance and ease of administration. Oral route is most preferred route by medical practitioners and manufacturer due to its highest acceptability by patients. About 60% of all dosage forms available are the oral solid dosage form. [1]

Oral films, also called oral wafers, are a group of flat films which are administered into the oral cavity. Today, Oral Thin Films are a accepted technology for systemic delivery of active pharmaceutical ingredients (APIs) for over-the-counter (OTC) medications and also for prescription drugs. [2]

Fast dissolving films are a oral drug delivery system that was developed based on the technology of the transdermal patch. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption. These films are prepared by hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, and deliver the medication to the systemic circulation via dissolution when comes in contact with liquid.

Fast dissolving oral film has emerged as an advanced alternative to the traditional tablets, capsules and liquids such as suspension, emulsion. These drug delivery system may allow the drug to bypass the first pass metabolism thereby making the medication more bioavailable. As the oral thin film dissolves, the drug can enter the blood stream through enteric, buccal or sublingually. [3]

Features of Fast Dissolving Oral Films

- This delivery system consists of a thin film shape and size like postage stamp.
- Fast dissolving oral films dissolves in the mouth like a cotton candy leaving pleasant mouth feel and acceptable taste.
- Fast dissolving oral film is unobstructed.
- After placing the films on the tongue, these get dissolves within seconds, by passing first pass metabolism as compared to conventional oral solid dosage forms, and may increase the bioavailability of drug.
- Fast dissolving oral film should leave minimum or no residue in the mouth after oral administration.
- Fast dissolving oral film should exhibit low sensitivity to environmental conditions such as temperature and humidity[4]

Advantages

- For improved patient compliance, these films are available in various size and shape
- Un-obstructive in nature
- Fast disintegration/dissolution time
- These films shows rapid onset of action and drug release
- Convenient dosing or accurate dosing
- No need of water to swallow or chew
- Ease of handling and transportation
- Controlled release of drug facilitates the rate and extent of absorption.
- Delivery of those API is possible which are at high risk of degradation in the gastrointestinal tract.

Disadvantages

- These films are hygroscopic in nature so must be stored in dry places, therefore special packaging are imperative in order to assure products stability and safety.
- Single packaging is recommended so every dose can be taken out individually; usually an aluminium pouch is used as packaging format.
- High dose of API cannot be incorporated into the oral film.
- The area of drug loaded FDOFs should be between 1-20 cm^2 and the drug can be loaded up to a single dose of about 30-40 mg.
- The drugs that having bitter in taste should be avoided or required taste masking.
- Proteinaceous drugs shouldn't be delivered, although co-administration of enzyme inhibitors such as aprotinin, bestatin, puromicin and bile salts is necessary to inhibit proteolytic salivary enzymes.
- Dose uniformity is a technical challenge.
- Even if the morphology of the film appears homogeneous and uniform distribution of drug is assured, the difficulty to obtain a high degree of accuracy with respect to the amount of drug in individual unit dose of the film can lead to therapeutic failure, non-reproducible effects and sometimes toxic effects to the patient.[5]

Formulation of Fast Dissolving Oral Films

Excipient should be chemically inert and approved for use in the formulation of oral films. According to the film forming material characteristics, the manufacture of the dosage forms can present different critical issues. Common problems are caused by foaming during the film formation due to the heating of the material or solvent evaporation, the flaking during the slitting and the cracking in the cutting phase. [6]

Table 1: Composition of oral thin films [7, 8]

S. No.	Name of the Excipient	Quantity
1.	Drug	5-30%
2.	Film forming polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva stimulating agent	2-6%
5.	Sweetening agent	3-6%
6.	Surfactant	Q.S
7.	Flavouring agent	Q.S
8.	Colouring agent	Q.S

Active Pharmaceutical Ingredients

The fast dissolving oral film technology has potential for delivery of variety of APIs. Since the size of the dosage form is limited, high dose of molecules are difficult to be incorporated into the films. Most of the 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 FDOFs. Multivitamins up to 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds.[9]

Suitable candidate for fast dissolving oral film are:

1. Drug should be potent having low dose
2. Drug should have no bitter taste
3. Good stability in water and pH of saliva and permeable through buccal mucosa.

Many APIs that can be potentially used for film technology are with bitter taste which makes the formulation unpalatable especially for pediatrics formulation. This requires the taste masking before incorporating the API in the fast dissolving oral films.

Various methods can be used to improve palatability of the formulation such as:

Obscuration Technique: The simplest method involves the mixing and blending of bitter tasting APIs with excipients of acceptable taste.

Barrier Technique: This method includes complexion, polymeric coating, and conversion into micro particles or microcapsules, coated particles or coated granules.[10]

Various categories of drug such as cardiovascular , antiemetic ,analgesics, ant allergic, antiepileptic, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, anti-Alzheimer's, expectorants, anti-tussive can formulated as film.[11]

Table 2: List of some marketed products along with their API [12]

S. No.	Drugs	API	Uses
1.	Benadryl®	Diphenylhydramine HCL (12.5mg or 25mg)	Antiallergic
2.	Suppress®	Menthol (2.5mg)	Cough suppressants
3.	Klonopin Wafers	Clonazepam (0.125mg,0.25mg,0.5mg, 1mg or 2mg)	In anxiety
4.	Theraflu®	Dextromethorphan HBR (15 mg)	Anti allergic
5.	Orajel®	Menthol/pectin (2mg/30mg)	Mouth ulcer
6.	Gas-X	Simethicone (62.5mg)	Anti flatuating
7.	Chloraseptic®	Benzocaine/menthol (3mg/3mg)	Sore throat
8.	Triaminic®	Diphenylhydramine HCL (12.5mg)	Anti allergic

Film forming polymer

The selection of polymer is one of the most important and critical parameter for the successful development of oral films because of their tensile strength which depends upon the type and amount of polymer used. At least 45% w/w of polymer should be present based on the total weight of dry film but typically 60-65% w/w of polymer is preferred to obtain desired properties. [13] The polymers can be used alone or in combination with other ingredients to obtain the desired film properties. The film obtained should be quiet enough so that there won't be any damage while handling or during transportation. [14]

Ideal properties of the film forming polymers

- The polymer employed should be non-toxic, non-irritant.
- It should be devoid of leachable impurities.
- It should have good wetting and spreading properties.
- The polymer should exhibit sufficient peel, shear and tensile strengths.
- The polymer should be readily available and should not be very expensive.
- It should have good shelf life.
- It should not aid in cause secondary infections in the oral mucosa/ dental region.
- It should have a good mouth feel property.
- It would be ideal to have a polymer that would have local enzyme inhibition action along with penetration enhancing property.
- It should not be an obstacle in the disintegration time.[15,16]

Table 3: List of polymers used in oral thin films [13,17]

Group	Class	Example
Natural	Carbohydrate	Pullalan, pectin, sodium alginate, maltodextrin, Sodium starch glycolate (SSG)
	Proteins	Gelatin
	Resin	Polymerized rosin (novel film former
Synthetic	Cellulose derivatives	Hydroxy propylmethycellulose (E3, E5, E15, K3, K15, K50), Methylcellulose (A3, A6, A15), Carboxy methylcellulose secekol- 30, Sodium carboxymethyl cellulose, Microcrystaline cellulose, Croscarmellose sodium (CCS).
	Vinyl polymer	Poly vinyl pyrrolidone (K-90, K-30), Poly vinyl alcohol, poly ethylene oxide
	Acrylic polymer	Eudragit (RD-100, 9, 10, 11, 12 and RL-100)

Plasticizer

Plasticizer is beneficial for preparation of FDF. Plasticizer helps to improve the flexibility of the film as well as reduces the brittleness of 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.[18] 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 the cracking, splitting and peeling of the film. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug. [19, 20]

The Plasticizers should impart the permanent flexibility to the strip and it depends on the volatile nature plasticizer and the type of interaction with the polymer. The properties of plasticizer are important to decrease the glass transition temperature of polymer in the range of 40–60 ºC for non-aqueous solvent system and below 75 ºC for aqueous systems. Plasticizer should be compatible with API as well as other excipients used for preparation of film. [21]

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. 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%w/w of weight of the strip. [22]

Sweetening agent

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations.

Suitable sweeteners include:

(a) Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose and stevioside, etc.

(b) Water soluble artificial sweetener: sodium or calcium saccharin salts, cyclamate salts and acesulfame-k, etc.

(c) Dipeptide based sweetener: aspartame

(d) Protein based sweeteners: thaumatin I and II.

The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, isomalt and maltitol can be used in combination as they additionally provide good mouth-feel and cooling sensation. Generally sweeteners are used in the concentration of 3 to 6 %w/w either alone or in combination. [23, 24]

Surfactant

Surfactants are used as solubilizing or wetting or dispersing agent so that the films gets dissolve within seconds and release the active agent instantly. Several numbers of surfactants are used in oral strip. One of the most important surfactant is poloxamer 407 that is used as solublizing, wetting and dispersing agent. Sodium lauryl sulfate is used in the formulation of mouth dissolving film of amlodipine. [25, 26]

Flavors

These are most important agents which are to be added to the pharmaceutical oral preparations because flavors are the ultimate goal for the choice of the preparations by the patients. It might have become the important factor for the sale of products. Both natural and artificial flavor are used. The amount of flavor required to mask the taste depends on the flavor type and its strength.

Preferably up to 10%w/w flavors are added in the formations. 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. [27]

Colors

A full range of colors is available, including FD&C colors, EU Colors, Natural Colors and custom Pantone matched colors. [28]

Pigments such as titanium dioxide or FD & C approved coloring agents are incorporated (notexceeding concentration levels of 1 percent; w/w) in Oral film when some of the formulation ingredients or drugs arepresent ininsoluble or suspension form. [29]

METHOD OF PREPARATION OF FAST DISSOLVING FILMS

Fast dissolving films can be prepared by:

a. Solvent casting method
b. Semisolid casting method
c. Hot melt extrusion
d. Solid dispersion extrusion
e. Rolling method

a. Solvent Casting Method [30]

In this method, water soluble polymers are dissolved in suitable solvent and the drug along with other excipients is dissolved in suitable solvent. Then both the solutions are mixed and stirred. This solution is then degassed under vacuum to settle the air bubbles. This bubble free solution is then finally casted into Petri plate and dried.

Advantage

• Great uniformity of thickness and great clarity than extrusion.
• Films have fine gloss and free from defect such as die lines.
• Films have more flexibility and better physical properties.

Disadvantages

• The polymer must be soluble in a volatile solvent or water.
• The stable solution with reasonable minimum solid content and viscosity should be formed.

b. Semisolid casting method [31]

In this method solution of water soluble film forming polymer is prepared. and resulting solution is added to a solution of acid insoluble polymer (Examples: cellulose acetate phthalate, cellulose acetate butyrate, etc). Then the appropriate amount of plasticizer is added to obtain a gel mass. This gel mass is then casted into the films or ribbons using heat controlled drums. The thickness of the films should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

c. Hot melt extrusion [32]

Hot melt extruder is used in this process. This technique involves shaping a polymer into a film via the heating process. A blend of pharmaceutical ingredients including API in dry state is filled in the hopper, conveyed, mixed and subjected to the heating process, and then extruded out in molten state melted by the extruder. The molten mass thus formed is used to cast the film. A critical step is the casting and drying process. This technique has many advantages, such as this process involves lower temperature and shorter residence times of the drug carrier mix, absences of organic solvents, continuous operation possibilities, minimum product wastage, good control of operating parameters and possibilities to scale up.

Advantages

• Improved bioavailability of poorly soluble compounds.
• During Processing solvents and water are not required.
• Cost-effective process with reduced production time and reduced number of unit operations.
• Homogeneous distribution of fine particle occurs.
• Sustained modified and targeted release capability.
• Superior stability at varying pH and moisture levels.
• Better content uniformity was obtained among granules of different size ranges.

Disadvantages

• Thermal degradation due to use of high temperature.
• Flow properties of the polymer are essential to processing.
• Limited number of available polymers.
• Require high power input.
• All excipients must be devoid of water or any other volatile solvent.
• Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates.
• Higher-melting-point binders require high melting temperatures and can contribute to volatility problems especially for heat-labile materials.

d. Solid dispersion

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. In this method drugs are dissolved in suitable solvents and then solutions are incorporated into the melt of polyethylene glycol below 70° C. Then solid dispersions are finally shaped into the films by means of dies. [33]

e. 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 cut in to 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. [34]

PATENTED TECHNOLOGIES [35]

a. XGel

XGel is at the heart of Meldex international's intellectual properties used in all its film system and its ingestible delivery technologies. XGel film Technology developed by BioProgress is bringing a revolution in the product offerings and manufacturing methods now available to the pharmaceutical industry. X Gel film, potentially enhance the product stability. It has also been developed for noningestible applications such as cosmetic, ostomy pouches, sanitary and healthcare devices. The development and manufacture of XGel films uses a means called "solution casting".

b. Soluleaves

In this technology, the film is produced in order to release the active ingredients on coming in contact with saliva. This is applied to flavor-release products such as mouth fresheners, confectionery and vitamin products. Soluleaves technology can be used to deliver active ingredients to oral cavity efficiently and in a pleasant and easily portable form. The delivery system can be used for the cough/cold, gastrointestinal and pain therapeutic areas as well as nutritional products. Soluleaves films can also be designed to adhere to mucous membranes and to release the active ingredients slowly over 15 minutes.

c**. Wafertab**

Wafertab is a drug delivery system that incorporates pharmaceutical actives into ingestible films. It is a patented delivery system that uses a unique process to prepare drug loaded thin films which can be used in topical or oral application. Active ingredients are incorporated into the film after casting. Wafertab system lends itself to many possibilities for innovative drug design, enabling multiple films with different actives to be bonded together.

d. Foamburst

Foamburst is a patent granted in September 2004 which is for capsules made of foamed film. Gas is blown into the film during production, resulting in a film with a honeycombed structure. The voids in the film may be gas-filled, empty or filled with other materials to produce specific taste burst characteristics or to deliver active drugs. The light honeycombed structure results in capsules that dissolve rapidly, causing a melt in-the mouth sensation. Foamburst has attracted from and confectionary manufactures as a mean of carrying and releasing flavors.

e. Micap

Micap signed an option agreement in 2004 to combine its expertise in microencapsulation technology with the Bio Progress water-soluble films. The developments aimed at providing new delivery mechanisms for the $1.4bn global market for smoking cessation products (SCPs).

CONCLUSION:

Fast dissolving oral films are non-bulky oral dosage forms that have several advantages over conventional ones which include the ease of administration with no need for water thus improving patient compliance particularly elderly and pediatrics. FDOFs are considered to be the most advanced, innovative and promising dosage forms as they have great potential

of delivering the medicinal agent systemically as well as locally. This emerging drug delivery system help in the effective management of immediate attacked diseases. Bypassing the hepatic first pass metabolism, fast dissolving films increase the bioavailability of the medication. However, mechanical properties of FDOFs are strictly influenced by polymeric composition so strip design and characterization is of paramount importance in order to improve drug efficacy.

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