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FAST DISSOLVING ORAL FILM- A REVIEW

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ABSTRACT

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. The FDOFs place as an alternative in the market due to the consumer's preference for a fast dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. However, for future growth point of view the oral thin film sector is well-positioned. In US market the OTC films of pain management and motion sickness are commercialized. More importantly, prescription FDOFs have now been approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. Today, FDOFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter(OTC) medications and are in the early- to mid-development stages for prescription drugs.

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INTRODUCTION

Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. Fast- dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experiences difficulties in swallowing traditional oral solid-dosage forms.Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after

the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [1].

Fast dissolving oral films also have an established shelf-life of 2-3years, depending on the API but are extremely sensitive to environmental moisture [2].

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at $500 million in 2007 and could reach $2 billion in near future according to Technology Catalysts [3].

The Fast dissolving oral films place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets/capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfills all the need of patients. Eventually, film formulations having drugs will be commercially launched using the Oral Thin Film technology [4].

This delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva,the film rapidly hydrates and adheres on to 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[5].

Special features of fast dissolving oral films[6]:

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

Advantages [6]:

Fast dissolving film combines all the advantages of tablets (accurate dose, self administeration) with those of liquid dosage forms (easy swallowing, quick bioavailability).

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity and the promote the systemic absorption of APIs
2. No need of water or a spoon for administration and without chewing
3. Dose accuracy in comparison to syrups
4. Rapid onset of action
5. The drug enters the systemic circulation with reduced hepatic first pass effect
6. Lower doses
7. Destructive acidic environment of stomach can be avoided
8. Minimal side effects
9. Site specific action and local action
10. Noninvasive

Disadvantage[7]:

1.The disadvantage of OTF is that high dose cannot be incorporated into the strip. Hence researchers have proven that the concentration level of active can be improved up to 50 percent; per dose weight.Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip.

2.Expensive packaging of oral film.

Composition of the Formulation [8,9,10]:

Oral dissolving film is a thin film with an area of 1-20 cm^2 (depend on dose and drug loading) containing drug. Drugs can be loaded up to a single dose of 30mg. Formulation considerations (plasticizers etc.) have been reported as important factors affecting mechanical properties of the films. A typical composition contains the following

Drug	5% to30%w/w
Water soluble polymer	45%w/w
Plasticizers	0-20%w/w
Surfactants	q.s.
Sweetening agent	3 to 6 %w/w
Saliva stimulating agent	2 to 6%w/w
Fillers, colors, flavors etc.	q.s.

1) Drugs[11,12]:

Several class of drugs can be formulated as mouth dissolving films including antiulcer (e.g. omeprazole),antiasthamatics (salbutamol sulphate), antitussives,expectorants, antihistaminics, NSAID'S (e.g.paracetamol, meloxicam, valdecoxib)

2)Water Soluble Polymers [13]:

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 mouthfeel and mechanical properties to the films.The disintegration rate of the polymers is decreased by increasing the molecular weight of polymer film bases.Some of the water soluble polymers used as film former are HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, Polyvinylpyrollidone PVP K-90, Pectin, Gelatin, Sodium, Alginate, Hdroxypropylcellulose, Polyvinyl alcohol,Maltodextrins and Eudragit RD108,9,10,11,12 Eudragit RL 100,Polymerized rosin is a novel film forming polymer.

3) Plasticizers[14]:

Formulation considerations (plasticizer, etc.) have been reported as important factors affecting mechanical properties of films.The mechanical properties such as tensile strength and elongation to the films have also been improved by the addition of plasticizers. Variation in their concentration may affect these properties.The commonly used plasticizers are glycerol, di-butylpthallate, and polyethylene glycols etc.

4) Surfactants[15]:

Surfactants are used as solublising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately.Some of the commonly used are sodium lauryl sulfate,benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent.

5.Sweetening Agents [16,17]:

Natural Sweeteners

The classical source of sweetener is sucrose,dextrose, fructose, glucose, liquid glucose and isomaltose.Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener.Polyhydric alcohols such as sorbitol, mannitol and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation.

Artificial Sweeteners

The artificial sweeteners can be classified in I generation and II generation sweeteners which are given below in table. 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.

6.Saliva Stimulating Agent [18]:

More saliva production helps in the faster disintegration of the fast dissoving film formulations so the formulations may contain acids which are used in the preparation of food 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.

7. Flavour[19]:

Any flavor can be added, such as intense mints, sour fruit flavors or sweet confectionery flavors.The amount of flavor needed to mask the taste depends on the flavor type and its strength.

8.Color [20]:

Pigments such as titanium dioxide or a full range of colors are available, including FDandC colors, EU Colours, Natural Colours and custom Pantone-matched colours.

MANUFACTURING METHODS:

One or combination of the following process can be used to manufacture the mouth dissolving films.

i) Solvent casting
ii) Semisolid casting
iii) Hot melt extrusion
iv) Solid dispersion extrusion
v) Rolling

But the most commonly used industrial methods are solvent-casting method and Hot melt extrusion.

Solvent-casting method : The OTF is preferably formulated using the solventcasting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed

to dry, which is then cut into pieces of the desired size.

Ex;A. Mahesh *etal.*[23] formulated levocetirizine.2HCl oral film with pullulan polymer by using solvent casting method. The optimized films of levocetirizine dihydrochloride were obtained.

Hot Melt Extrusion : In present method the mass is prepared first under the control of temperature and steering speed. Afterwards, the film is coated and dried in a drying tunnel, once again the temperature, air circulation and line speed are controlled. Then follows a slitting and in the last step the films are punched, pouched and sealed.

Ex. F. Cilurzo *etal.*[24] formulated Piroxicam film with Maltodextrin plasticized by glycerin by using Hotmelt extrusion method.

Semisolid Casting : In this method solution of water soluble film forming polymer are mixed to solution of acid insoluble polymer to form homogenous viscous solution (e.g. cellulose acetate phthalate, cellulose acetate butyrate).After sonication it is coated on non-treated casting film. On drying The thickness of the film is about 0.381-1.27 cm. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

Solid Dispersion Extrusion : Solid dispersions are prepared by immiscible components and drug. Finally the solid dispersions are shaped in to films by means of dies.

Rolling Method : In this 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 gives desired shape and size [25].

EVALUATIONS PARAMETERS :

1) Mechanical properties : Mechanical properties of films are evaluated Instron using a TA.XT2 texture analyzer equipment equipped with a 5kg load cell. Films are held between two clamps positioned between 3cm. During measurement the strips were pulled at rate of 2mm/sec. The force and elongation were measured when film breaks.Three mechanical properties namely tensile strength,elastic modulus and % elongation are calculated[26].

a) Tensile strength : Tensile strength is calculated by formula =force at break/ initial cross-sectional area of film in mm2

b) Elastic modulus : Elastic modulus is calculated by formula

$$\text{Elastic modulus} = \frac{\text{force at corresponding strain}}{\text{Cross sectional area (mm2)}} \times \frac{1}{\text{Corresponding strain}}$$

c) % Elongation

$$\text{It is calculated as} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

d) Folding endurance

Folding endurance is determined by folding the films of uniform cross sectional area and thickness until it breaks.

2) Morphology study : The morphology of the films is studied using scanning electron microscopy (SEM), at a definite magnification[27].

3) Thickness : The thickness of the strip can be measured by micrometer screw guage at different strategic locations.This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of the dose in the strip.

4) Surface pH of film : Surface pH of films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films.The change in color of pH paper was observed and reported[28,29,].

5) Assay /drug content and content uniformity : This is determined by any standard assay methiod describe for the particular API in any of the standard pharmacopoeia.Content uniformity is determined by estimating the API content in individual strips.Limit of content uniformity is 85%-115%.

6) Organoleptic Evaluation : Since the OS are intended to disintegrate rapidly or reside for duration of time in the oral cavity,the product needs to have acceptable organoleptic palatable characteristics.The product should possess the desired features of sweetness and flavor which is acceptable to large mass of population.For psychophysical evaluaton of the product,special

controlled humans panels are used.In-vitro methods of utilizing taste sensors,specially designed apparatus and drug release by modified pharmacopoeial methods are being usedfor this purpose.These in-vitro taste apparatus and methodologies are well suited for high throughput taste screening of oral pharmaceutical formulation[30].

8) *In vitro* disintegration time : *In vitro* disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec.The disintegration time is the time when the film starts to break or disintegrates[31].

9) In vitro dissolution studies : The in vitro dissolution study is carried out in simulated saliva solution pH 6.4 phosphate buffer using USP paddle apparatus at 37±0.5°C.Samples are withdrawn at regular time interval and analyzed by UV-Visible spectrophotometer[31].

Packaging : A variety of packaging options are available for fastdissolving films.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[32].

Marketed Films

List of marketed fast dissolving films

Sr.No.	Product	Manufactured by
1.	Dextromethorphan HBr (cough s uppressant), Diphenhydramine Citrate (cough and cold),Breath Strips	MonoSolRx
2.	Doneprezil rapid dissolving films, Ondansatron rapid dissolving films	Labtec Pharma
3.	Life-saving rotavirus vaccine to infants	Johns Hopkins undergraduate biomedical engineering students
4.	Methylcobalamin fast dissolving films, Diphemhydramine HCl,fast dissolving films,Dextromethorphan fast dissolving films,Folic Acid 1mg fast dissolving films, Caffeine fast dissolving films.	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 consumer healthcare.

CONCLUSION:

The present review conclude that fast dissolving oral film is most acceptable and accurate oral dosage form which bypass the hepatic system and show more therapeutic response.The pharmaceutical companies prefer this dosage form due to both patient compliance (especially pediatric and geriatric) as well as industrial acceptability.Oral films can replace the over-the-counter (OTC) drugs, generic and name brand from market due to lower cost and consumer‘s preference.Fast dissolving oral films have several advantages over the conventional dosage forms. So they are of great importance during the emergency cases such as allergic reactions and astahmatic attacks whenever immediate onset of action is desired.

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