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FAST DISSOLVING FILM REVIEW

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Abstract:
Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The film is an ideal intra oral fast-dissolving drug delivery system. A large number of drugs can be formulated as mouth dissolving films, for example neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction etc. There are many techniques were available to prepare the oral films at the buccal cavity. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The present review provides an account of various formulation considerations, method of preparation and quality control of the oral fast dissolving films.

***Key words**: Oral Fast Dissolving Film, Buccal Cavity, , High Permeability, Better Patient Compliance.*

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INTRODUCTION:

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements 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 .

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.[2] These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. 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.[3]

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. 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 .[4]

Special features of mouth dissolving films

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

The ideal characteristics of a drug to be selected

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose upto 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 be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Advantage of orally fast dissolving films

Oral dissolving films can be administered without water, anywhere, any time.

- Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity.
- Oral dissolving films are flexible and portable in nature so they provide ease in transportation, during consumer handling and storage.
- 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.
- Beneficial in cases such as motion sickness, acute pain, suede episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- 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.
- As compared liquid formulations, precision in the administered dose is ensured from each strip of the film.
- 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.
- 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.

- Provide new business opportunity like product differentiation, product promotion, patent extension.

Disadvantages

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Taste masking- Most drugs have bitter taste, and need taste masking.
- Special packaging- OFDFs are fragile and must be protected from water so it needs special packaging.

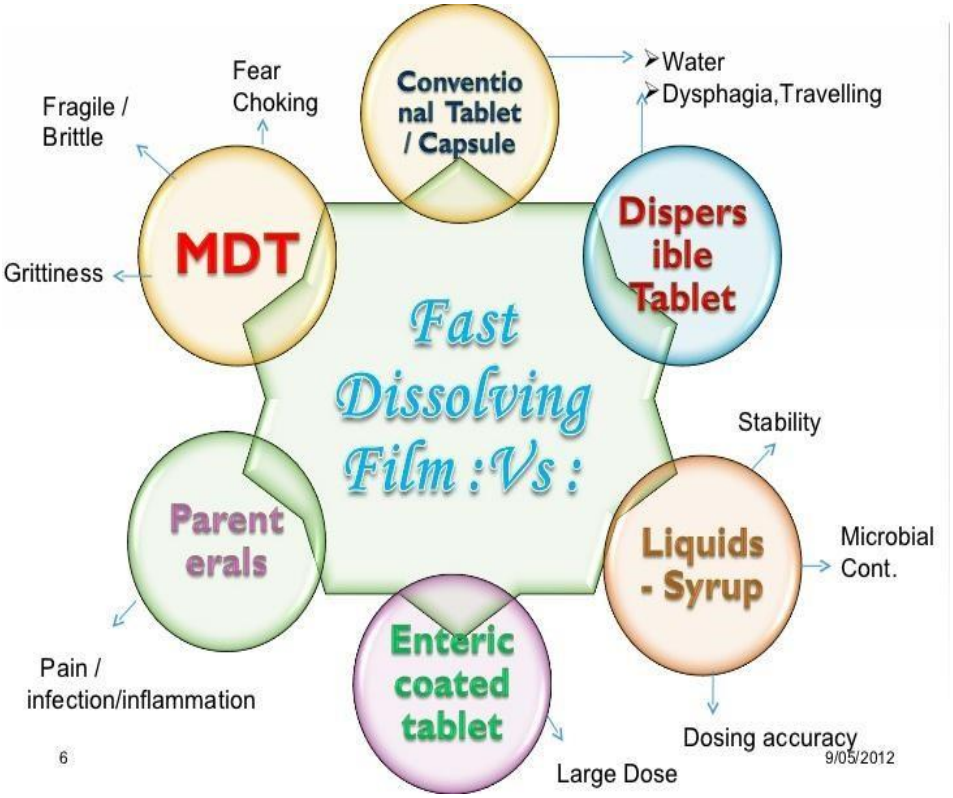

Figure 1: Comparison of fast dissolving oral film over other dosage forms.

Formulation of fast dissolving film:

Active ingredients:

The film composition contains 1-30% w/w of the active pharmaceutical ingredient. Always use low dose active pharmaceutical ingredients because high dose of drug are difficult to incorporate in fast dissolving film. A number of drugs can be used as fast dissolving oral film including anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, antiemetic, etc[5,6]. Dimenhydrinate can also be incorporated into ODFs for taste masking. Common examples of drugs incorporated into ODFs are salbutamol sulfate, rizatriptan benzoate, verapamil, ondansetron, dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc.

2.Film-Forming Polymers

Polymers are the most important ingredient of the fast dissolving oral film. Robustness of the film depends on the amount of polymer added in the oral strip. Generally, 45% w/w of polymer is used which is based on total weight of dry film. The selection of polymer is one of the most important and critical parameters for the successful development of oral films because of their tensile strength which depends upon the type and amount of polymer used. Mainly hydrophilic polymers are used in the oral strip as they rapidly disintegrate in the oral cavity as they come in contact with saliva. Currently, both natural & synthetic polymers are used for the preparation of fast dissolving film.[7]

3. **Plasticizer**
Plasticizer helps to improve the flexibility and reduces the brittleness of the strip by reducing the glass transition temperature of the polymer. The selection of plasticizer depends on its compatibility with the polymer and the type of solvent used in the formulation.[8] Commonly used plasticizers are glycerol, propylene glycol, low molecular weight polyethylene glycols (PEGs), phthalate derivatives like dimethyl, diethyl, and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil. The plasticizers concentration of 0–20 % w/w of dry polymer weight is used by avoiding the film cracking, splitting and peeling of the strip. The use of certain plasticizers may also affect the absorption rate of the drug. The properties of plasticizer are important to decrease the glass transition temperature of the polymer in the range of 40-60ºC for a nonaqueous solvent system and below 75 ºC for aqueous systems. Cellulosic hydrophilic polymers were easily plasticized with hydroxyl-containing plasticizers like PEG, propylene glycol, glycerol, and polyols.[9] In contrast, less hydrophilic cellulosic polymers were plasticized with esters of citric acid and phthalic acid. Glycerol acts as a better plasticizer for polyvinyl alcohol while diethylene glycol can be used for both Hypromellose as well as polyvinyl alcohol films.

4. **Surfactants:**
Surfactants are used as a wetting or solubilizing or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Commonly employed are poloxamer 407, benzethonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactants is poloxamer 407. [10]

5. **Sweetening agents:**
Sucrose is the most commonly used sweeteners in FDOFs. Sucrose is very soluble in water and being colorless does not impart any undesirable color to the final formulation. Some of the commonly employed sweeteners are dextrose, sucrose, fructose, glucose, isomaltose, polyhydric alcohols (sorbitol, mannitol), etc.[11] Artificial sweeteners like saccharin, cyclamate, aspartame (first generation), sucralose, alitame and neotame (second generation) can also be used.

6. **Saliva stimulating agents:**
Saliva stimulating agents are used to increase the rate of production of saliva that would help in the faster disintegration of the rapid dissolving strip formulations. Examples of salivary stimulants are citric acid, malic acid, lactic acid, ascorbic acid and

7. **Flavouring agents:**
Flavours used in the formulation must be non-toxic, soluble, stable and compatible with the excipients. The quantity of flavouring agent required to mask the taste depends on the flavour type and its strength.[14]

8. **Colouring agents:**
Generally incorporated colouring agents have FD&C approved colours, natural colours, pigments such as titanium dioxide etc. The colouring agents should not exceed concentration levels of 1%w/w. [15]

Manufacturing Methods:
There are five methods which are used alone or in a combination with the following process for the manufacture of the fast dissolving oral films.

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

Solvent-casting method
The OTF is preferably formulated using the solvent casting method, whereby the watersoluble 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. [16,17]
Advantages:

- Better uniformity of thickness and better clarity than extrusion.
- Film has fine gloss and freedom from defects such as die lines.

Disadvantages:

- The polymer must be soluble in a volatile solvent or water.
- A stable solution with a reasonable minimum solid content and viscosity should be formed.
- Formation of a homogeneous film and release from the casting support must be possible.

Hot Melt Extrusion
In the present method, the mass is prepared first under the control of temperature and steering speed. Afterward, the film is coated and dried in a drying tunnel, once again the temperature, air circulation, and line speed is controlled. Then follows a slitting and in the last step the films are punched, pouched and sealed.[18,19]

Advantages:

- Without the use of any solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- A better alternative for poorly soluble drugs.
- More uniform dispersion because of intense mixing and agitation.
- Less energy compared with high shear methods.

Disadvantages:

- Thermal degradation due to use of high temperature
- Flow properties of the polymer are essential to processing
- A limited number of available polymers
- All excipients must be devoid of water or any other volatile solvent

Semisolid Casting

In this method solution of a water-soluble film-forming polymer are mixed to a solution of the 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.[20]. 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 into films by means of dies.[21]

Precautions while preparing sold dispersions:

The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol and polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.[22]

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.[23]

EVALUATIONS

1. **Weight Uniformity:**
   Films can be weighed on analytical balance and average weight can be determined for each film. It is useful to ensure that a film contains proper number of excipients and drug.[24]

2. **Thickness:**
   The thickness of film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.[25]

3. **Dryness Test/Tack Tests:**
   About eight stages of film drying process have been identified and they are set-to touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat dry print free. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.[26]

4. **Tensile Strength:**
   Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the film as given below: [27]

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{Film width}}$$

5. **pH value:**
   The pH value can determine by dissolving one oral film in 10ml distilled water and measuring the pH of the obtained solution. It is necessary that film should have nearly uniform pH.[27]

6. **Tear resistance**:
   Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically, very low rate of loading 51 mm (2 in.)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds-force).[28]

7. **Young's modulus:**
   Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows: [29]

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Stripthickness} \times \text{Crossheadspace}}$$

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

8. **Folding endurance:**
Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.[30]

9. **Disintegration time:**
The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30s.[31]

10. **Dissolution test:**
Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API . Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.[32]

11. **Assay/drug content and content uniformity:**
This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115 percent.[33]

12. **Organoleptic evaluation:**
For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. *In-vitro* methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These in-vitro taste assessment apparatus and methodologies are well suited for high throughput taste screening of oral pharmaceutical formulations.[34]

Future prospect:

In the pharmaceutical industry, great advancements have been made in oral drug delivery technologies. The market has come a long way from the conventional tablets/capsules to modern-day fast disintegrating and rapidly acting tablets/films. Various limitations such as lower bioavailability of oral solid drugs, the inconvenience of administering injections, inaccurate dosing by liquid formulations are keystone which has turned the focus of pharmaceutical companies to develop novel oral dosage forms that eliminate these limitations.[35] Fast dissolving oral thin films are designed to meet most of these challenges. The concept isn't new and several over the counter oral thin films are readily available. Good acceptance from the users and an increasing demand of over the counter oral film products has led to the development of prescription drugs into oral thin films. This emerging area is gaining attention from both established and start-up pharmaceutical firms. Companies are utilizing their oral thin film technologies to develop different types of oral thin films (e.g. oral dispersible, sublingual, buccal). In addition to the drugs, several hormones and vaccines are also being formulated into oral thin films with the aim of providing improved patient compliance. Some of the key players in this area include MonoSol Rx, Applied Pharma Research/Labtec GmbH, BioDelivery Sciences and NAL Pharma.[36] Many companies are collaborating with these technology providers and utilizing oral thin films as a lifecycle management tool for their branded drugs that have lost patent in other dosage forms. There are not many prescriptions for oral thin films currently available in the market; however, the pipeline holds a wider promise. Despite the uncertainties related to the development, approval and penetration rate, the market is likely to witness stable growth in the coming decade. According to the clinical and regulatory aspects in the US Food and Drug Administration (US FDA), if the product is bioequivalent to that of the existing oral product the drug, an Abbreviated New Drug Application (ANDA) route is followed. There are no clinical studies associated with this generic approval processes (section 505 (j) of the Food, Drug, and Cosmetic Act). The example of such case would be a comparative bioequivalence between an orally disintegrating tablet (ODT) formulation and orally dissolving film (ODF) product. However, developed oral film product may exhibit different pharmacokinetic profile compared to the existing marketed product. The ODF is categorized as "new dosage form" and the section 505 (b) (2) approval processes needs to be followed. In this case, a new clinical study would be required.[37] The advantage of new clinical study is that it would award 3 years of marketing exclusivity to the product. Preclinical toxicity studies are not required if the molecule is the same as that of the approved product. Safety, tolerability, and efficacy features are to be demonstrated in such trials. Oral mucosa-irritation testing is carried out in both animal models and humans. The future looks very promising for the film technology in the time to come as new technologies are rapidly introduced to prepare thin films.[38]

CONCLUSION:

Recently Fast dissolving films have gained popularity as dosage forms for the mouth Fresheners Meanwhile pharmaceutical industries have recognized their potential for delivering medicinal products and have launched several products for the OTC market using this technology. The fast dissolving thin film are hardly described and investigated in literature, but seem to be an ideal dosage form for use in young children, especially in geriatric and pediatric patients. They combine the greater stability of a solid dosage form and the good applicability of a liquid. Due to lack of standard methodology for preparation and analysis products existence in the market is limited.

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