

AN OVERVIEW ABOUT NOVEL FAST DISSOLVING ORAL FILMS

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REVIEW ARTICLE

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ABSTRACT

Nowadays, novel fast dissolving oral films (FDF) have come in existence as an alternative dosage form in comparison with tablet, capsules, syrup and other oral dosage forms with respect to patient convenience and compliance. Fast dissolving oral films are helpful to paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. The FDF drug delivery systems are solid dosage form which disintegrate or dissolve within seconds when placed in the mouth cavity without need of water or chewing. FDF provide better drug dissolution, faster onset of action, bypassing the first pass metabolism of drugs and thus enhance their oral bioavailability with reduced dosing frequency. These formulations are suitable for cough, cold, sore throat, allergenic conditions, nausea, pain, hypertension and CNS disorders. The present review provides the details about the recent advancement in design and development of oral fast dissolving film.

Keywords: Fast dissolving oral film, Bioavailability, Solvent casting technique, Plasticizer.

INTRODUCTION

Fast or quick dissolving oral dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. (1) They undergo rapid disintegration in the salivary fluids of oral cavity within seconds, where they release the active pharmaceutical ingredient. (2, 3) The large amount of drug is swallowed orally with the saliva where subsequent absorption takes place in the GIT. They are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms.(4, 5) It gives quick absorption and bioavailability of drugs due to high blood flow and permeability of oral mucosa of 4-1000 times greater than that of skin. This is useful in patients such as diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful where local action is desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. (6, 7)

Mechanism of absorption through oral mucosa

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular (intercellular, passing around the cell) and transcellular (intracellular, passing through the cell) routes. Drugs can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the drugs. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces are the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

Ideal characteristics of FDF (8-10)

- Should be thin and elegant.
- Should have a pleasant mouth feel.

- Should be available in various size and shapes.
- Should have fast disintegration without water and rapid drug release.
- Should be compatible with taste masking.
- Should leave minimum or no residue in the mouth after oral administration.
- Should have low sensitivity to environmental conditions such as temperature and humidity.

Advantages of FDF (2, 11)

- Ease of administration to paediatric, geriatric, and psychiatric patients who cannot swallow tablets and other solid dosage forms.
- No need of water for swallowing.
- Rapid dissolution and absorption of poorly water soluble drugs, which produce rapid onset of action.
- Pregastric absorption can result in increased bioavailability with reduced dosage; improved clinical performance through a reduction of unwanted effects.
- Taste masking is possible for bitter drugs.
- Useful in cases where rapid onset of action required such as in motion sickness, sudden allergic attack or coughing, hypertension, bronchitis or asthma.
- More economical

Ideal characteristics of drug candidate for FDF (12)

- ✓ It should have low dose less than 40mg.
- ✓ Drugs with low molecular weight drugs are preferred.
- ✓ It should possess pleasant taste.
- ✓ It should have good stability in water as well as saliva.
- ✓ It should be partially unionized at pH of the buccal cavity.
- ✓ It should have the ability to permeate the oral mucosal tissue.

Limitations of FDF (2)

- Drugs which are unstable at buccal pH cannot be administered.

- Only small dose drug can be administered due to limited surface area of buccal cavity.
- Stability problems like moisture sorption and brittleness during storage.

FORMULATION CONSIDERATIONS

Formulation additives

1. Active pharmaceutical ingredient

Various categories of drugs such as antiemetic, neuroleptics, antihypertensives, cardiovascular agents, analgesics, antiallergic, antiepileptics, anxiolytics, sedatives, hypnotics, diuretics, antiparkinsonisms, antibacterials, anti-alzheimers, expectorants, antitussive and drugs used for erectile dysfunction can be incorporated in FDFs. (1, 13-15)

2. Film forming agents

For the preparation of FDF various hydrophilic polymers can be used in the film formulation upto 40% w/w of the film content. The polymers are responsible for the overall strength of the film. The film should be tough to prevent damage during handling and transportation. The polymers are hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), starch, modified starch, pullulan, gelatin, carboxy methyl cellulose, polyvinyl pyrrolidone (PVP), cross linked PVP, alginates, poly vinyl alcohol, maltodextrose and polyox. (9,16)

Among this the pullulan and HPMC are the best suitable polymers for the preparation of FDF. Pullulan is a neutral glucan (like amylose, dextran, cellulose), with a chemical structure somewhat depending on carbon source, producing microorganism, fermentation conditions. HPMC is propylene glycol ether of methylcellulose and its low viscosity grades are used for the preparation of FDF like HPMC E3/E5/E6/E15. (17, 18)

3. Plasticizer

Plasticizer helps to improve the flexibility of the film and reduces the brittleness of the 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. (19,20) Propylene glycol (PG), polyethylene 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. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug. (21, 22)

4. Disintegrating agents

Disintegrating agents are added to FDF formulations to promote its breakup into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. Substances like microcrystalline cellulose, sodium starch glycolate, cross povidone and Ac-Di-Sol are used alone or in combination.

5. Flavoring agents

Both natural and artificial flavor used such as artificial vanilla, cinnamon, various fruit flavors, mints such as peppermint, menthol, essential oils such as thymol, eucalyptol and methyl salicylate may be either individual or combination. (9)

6. Sweetening agents

Natural sweeteners include monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose, mannose, galactose, fructose, dextrose, sucrose, maltose, partially hydrolyzed starch, or corn syrup solids and sugar alcohols such as sorbitol, xylitol, mannitol may be used. Water soluble artificial sweeteners such as the soluble saccharin salts, cyclamate salts, acesulfam-K and dipeptide based sweeteners. Aspartame, neotame are also used successfully for the taste masking. (23, 24)

7. 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 FDF. Generally acids which are used as salivary stimulants citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants and citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%. (25)

8. Cooling agents

Monomethyl succinate is used as cooling agent and it helps to improve the flavor strength to enhance the mouth feel effect of the product. Other cooling agents like WS3, WS23 and Utracoll-II can also be used in conjunction with flavors. (25)

9. Coloring agents

Titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in FDF formulation when some of the formulation ingredients or drugs are present in insoluble or suspension form. (25)

10. Surfactants

Surfactants are used as solubilising or wetting or dispersing agent. By the use of surfactant the film gets dissolved within seconds and release active agent immediately. Solubility of poorly soluble drugs in fast dissolving oral films can be improved by using surfactant. Some of the examples are polaxamer 407, sodium lauryl sulphate, benzalkonium chloride, benzthonium chloride, tweens and spans. (25)

11. Stabilizing and thickening agents

Stabilizing and thickening agents are employed before casting to improve the viscosity and consistency of dispersion or solution of the film preparation. Natural gums like xanthan gum, locust bean gum, carragenan and cellulosic derivatives are few examples of stabilizing and thickening agents. They are used in the concentration up to 5%w/w. (25)

Methods of preparation of FDF

One or more of the following process can be used to manufacture the fast dissolving oral films.

1. 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 into the petri plate to form film and dried. (13, 26)

2. 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 are cellulose acetate phthalate and cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4. (13, 26)

3. 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 15rpm in order to process the granules inside the barrel of the extruder for approximately 3-4 min. The processing temperatures should be 80°C (zone-1), 115°C (zone-2), 100°C (zone-3) and 65°C (zone-4). The extrudate then pressed into a cylindrical calendar in order to obtain a film. (27, 28)

4. 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. (27, 28)

5. 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 cut into desired shapes and sizes. (27)

6. Spray drying technique

A solvent system containing film former and other excipients are sprayed or coated on suitable carrier material, dried and peeled off to get the film. The carrier materials used for film are glass, non siliconized kraft paper or polyethylene film.

Evaluation of FDF (3, 28-30)

1. Morphology study

The morphology of the films can be observed using scanning electron microscopic (SEM) at definite magnification.

2. Dryness/ Tack test

Dryness is the property to measure the solvent or water content present in the film whereas tack is the tenacity with which the film adheres to any piece of paper which is pressed into contact with the strip. Eight stages of film drying process have been recognized i.e. set-to-touch, dust free, tack-free, dry-to-touch, dry-hard, dry-through; dry-to-recoat & dry print free.

3. Weight variations

Weight variation can be determined by individually weighing 10 randomly selected films and calculating the average weight of the films. The average weight should not deviate significantly from the weight variation limit.

4. Thickness

The thickness of film is determined by screw gauge or micrometer at different points of the films.

5. Drug content

A film of 2 cm² size is cut and put into volumetric flask containing solvent. This is then shaken in a mechanical shaker for 2hrs to get a homogeneous solution and filtered. The drug content is determined by UV spectrophotometer after appropriate dilution.

6. Tensile strength

Tensile strength of films can be determined using an apparatus fabricated in laboratory. A small film (2cm²) is cut and fixed to assembly. The weight required to break the film is noted and simultaneously film elongation is measured with the help of pointer mounted on the assembly.

Tensile strength = break force /ab (1+ ΔL/L)

Where a, b and L are width, thickness, and length of the strip, and ΔL is the elongation at break.

7. Transparency

To determine transparency of film, a simple UV spectrophotometer can be used. The film specimen is placed on the internal side of spectrophotometer cell. The transparency of films is calculated as follows:

$$\text{Transparency} = (\log T_{600})/b = -\epsilon c$$

Where T_{600} is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

8. Percentage elongation

It can be determined by noting the distance travelled by pointer before break of the film on the graph paper.

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{original length}} \times 100.$$

9. Percentage moisture loss

To determine percentage moisture loss films of area 2 cm^2 are cut and weighed accurately. After weighing, the films were kept in desiccators containing fused anhydrous calcium chloride. The films should be kept for 72 hrs in the desiccator. After 72 hrs, they are taken out and again weighed and the percentage moisture loss of films was measured by using the formula:

$$\text{Percent moisture loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

The percentage moisture loss studies are done to determine physical stability and integrity of the film.

10. Folding endurance

It involves determination of the folding capacity of the films when subjected to frequent extreme condition of folding. It is determined by repeatedly folding the film at same place until it broke.

11. Surface pH of film

Surface pH of the 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 the color of pH paper was observed

12. Disintegration test

It can be determined by dipping the film in 10ml of water in beaker with gently shaking when film was dissolved, time is noted.

13. In-vitro drug release

Dissolution testing can be performed using the 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 drug.

14. Stability studies

Stability study can be carried out for all the batches at accelerated condition 65% relative humidity and 35°C (temperature) in the humidity chamber for the three months. After 3 months the films are evaluated for the drug content, disintegration time and physical appearance observation.

Packaging of FDF

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving oral films. The material selected must have the following characteristics:

- They must protect the preparation from environmental conditions.
- They must be FDA approved.
- They must be non-toxic.
- They must meet applicable tamper-resistant requirement.
- They must not be reactive with the product.
- They must not impart to the product tastes or odours.

CONCLUSION

Oral route always remains the primary drug delivery route because of ease of administration with beneficial release characteristics and fast dissolving films are the novel, revolutionary approach in oral drug delivery system for all the

population groups, specifically geriatric, pediatric patients and patients with swallowing difficulties. FDFs are also having great potential of delivering the drug systemically as well locally with improved patient compliance, rapid onset of action, decreased dosing frequency by avoiding first pass metabolism, improved bioavailability and have several advantages over many dosage forms as well as offer easy production and evaluation technique. Based on the present review it can be concluded that delivery of drug into an elegant, stable and effective FDF formulation may bridges the gap between solid and liquid dosage forms.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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