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Fast Dissolving Oral Films; Various Formulation Methodologies, Evaluation and Current Approach

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ABSTRACT

Fast dissolving oral films is an emerging oral dosage form that was first developed in 1970. It is designed and formulated using hydrophilic polymers that rapidly dissolve on the tongue or in the mouth. Due to the high permeability of the buccal cavity than the skin, its bioavailability is quite greater and the first-pass metabolism is escaped. For the preparation of the film, many processes such as solvent casting, hot-melt extrusion, rolling, and solid dispersion have been reported in the literature. It is one of the best alternatives to another available dosage form for drug delivery. It greatly helps in overcoming the issue of swallowing in paediatric or geriatric patients who generally don't prefer any solid dosage form due to fear of choking. Unlike another oral solid dosage form, fast dissolving oral films do have the advantage that it does not require water for administration. This review reflects the formulation aspects, evaluation, and recent approaches adopted for fast dissolving oral films.

INTRODUCTION:

The oral route of drug administration is the most preferable with ease of handling for all age patients. Various research for new novel approaches for oral drug delivery led to the development of fast dissolving oral films. Fast dissolving oral films were developed as an alternative to other dosage forms in 1970[1]. Fast dissolving oral films are the new approach to delivering drugs to the patients with increased bioavailability, quick onset of action and avoiding the first-pass metabolism. The permeability of oral mucosa is 4-1000 times greater than that of skin[2]. The motto behind the development of such dosage form was to overcome the problem of swallowing in pediatric and geriatric patients. It is a combination of API, hydrophilic polymer with other excipients like sweetener, flavour, colour, binder, stabilizing agent, saliva stimulating agent, preservative, etc. Hydrophilic water dissolving polymers like Pullulan, Gelatin, Sodium Alginate, Pectin, Rosin, Starch, Chitosan, and cellulose ethers are used to facilitate fast dissolving in the buccal cavity or on the tongue[3].

Recent development in technology has presented numerous dosage forms for the oral route, of which mouth dissolving oral films have got great acceptance due to ease of use and no use of water. These are the thin strips that could be placed on the tongue of the patient by which it gets dissolved with the help of saliva and reaches the site. The manufacturing of fast dissolving oral films are quite cost-effective compared to a tablet, capsules, syrups, etc. FDOFs offer fast and accurate dosing. The only major disadvantage associated with FDOFs is high doses cannot be incorporated into the films. There is no specific dissolution procedure available for fast dissolving oral films. But, a study indicates two different methods to check the dissolution time of oral films. Method I; Add a single drop of water to the oral film and record the time required to dissolve that part and form a hole on the film. Method II; Add 2 ml of water to a Petri plate and put the oral film on the surface of the water and record the time required to dissolve fully the oral film. Five readings are taken and the average was calculated for the actual time required for dissolution[4]. The findings of oral film dosage form will increase compliance of the patient of all ages, increase the bioavailability of the drug, and avoid the first-pass metabolism thus reducing the frequency of doses. Table 1 indicates the list of available fast dissolving oral films[5,6].

EVOLUTION OF FAST DISSOLVING ORAL FILMS

Fig 1 describes the Evolution of fast dissolving oral films.

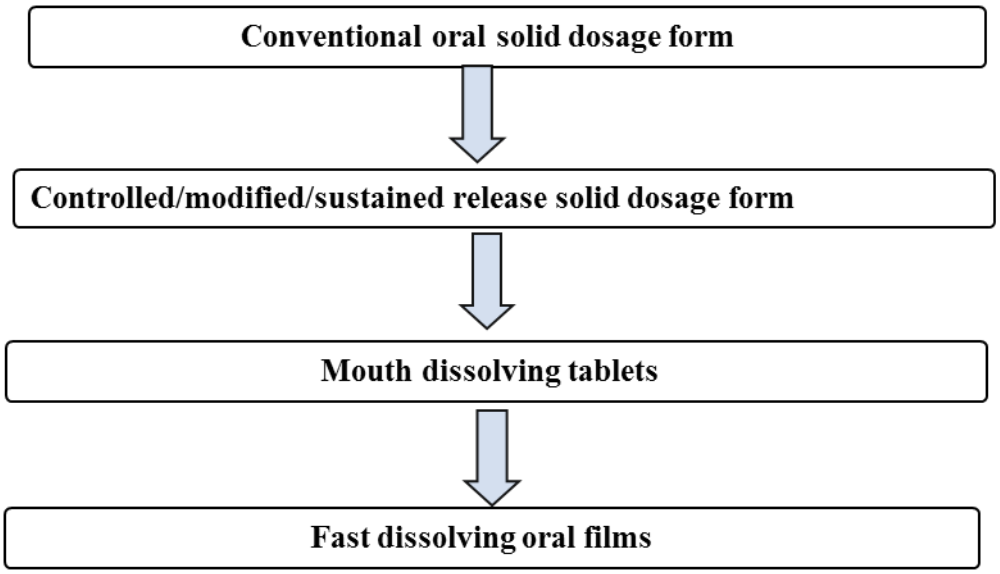

Fig 1: Evolution of fast dissolving oral films

FEATURES OF FAST DISSOLVING ORAL FILMS

- Fast dissolving
- Ease of use
- Ease of manufacture
- Rapid release
- Availability in various sizes and shapes
- Feasible for pediatric and geriatric patients

Table 1 enlists the marketed products of the fast dissolving oral films.

Table 1: Marketed products of the fast dissolving oral films

Sr No	Product	API	Manufacturer	Use
1	Listerine	Cool mint	Pfizer	Mouth ulcer
2	Benadryl	Diphenehydramine HCL	Pfizer	Anti-allergic
3	Theraflu	Dextromethorphan	Novartis	Anti-allergic
4	Chloraseptic	Benzocain/menthol	Prestige	Sore throat
5	Triaminic	Diphenhydramine	Novartis	Anti-allergic
6	B12 Film	Methylcobalamine	Shilpa medicare	Vitamin
7	Gas-X	Simethicone	Novartis	Antiflatuating

FORMULATION INGREDIENTS

Formulation of fast dissolving films: -

Fast dissolving oral films include various ingredients for their formulation such as

- Active pharmaceutical ingredient (5-30%)
- Film-forming polymers (40-50%)
- Plasticizer (1-10%)
- Sweetening agent (2-6%)
- Saliva stimulating agent (2-6%)
- Surfactants (Q.S)
- Flavoring agent (Q.S)
- Coloring agent (Q.S)

Active Pharmaceutical Ingredients

Various classes of drugs like antiulcer (eg. Omeprazole), antihistaminic (eg. Salbutamol), antitussive (eg. Dextromethorphan), expectorant, mouth fresheners (eg. menthol), NSAIDs (eg. Meloxicam) analgesics (eg. Dihydroetorphine), antiepileptic (eg. diazepam), anxiolytics, sedatives (eg. alprazolam), hypnotics (eg. Zolpidem Tartrate), diuretics (eg. furosemide),

anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction, can be formulated into oral films [7]. Usually, a small dose drug i.e potent drug is suitable for oral films.

The ideal characteristics of the drug to be selected[8-10]

- The drug should have a pleasant taste.
- The drug's therapeutic dose should not exceed 40 milligrams.
- The medicine should have a low molecular weight and a small molecular size.
- In both water and saliva, the drug should have adequate solubility and stability.
- At the pH of the oral cavity, it should be partially unionized.
- The drug should be resistant to changes in the environment.
- It should be permeable to oral mucosal tissue.

Water-soluble polymers

Polymers are generally film formers. Water-soluble polymers help the films to get easily and rapidly dissolve in the buccal cavity. The polymer in the oral films is decided based on its disintegration time. When the molecular weight of polymer film bases increases, the rate of disintegration of the polymers decreases. Some of the water-soluble polymers used as film former in oral films are HPMC, Methylcellulose, Pullulan, carboxymethylcellulose, Polyvinylpyrollidone, Pectin, Gelatin, Polyvinyl alcohol, Sodium Alginate, Hdroxypropylcellulose, Maltodextrins, etc[11].To achieve desirable qualities such as hydrophilicity, flexibility, mouthfeel, and solubility, polymers can be employed alone or in combination with two or more other polymers.

Plasticizers

The main role of plasticizers in fast dissolving oral film is to maintain flexibility to avoid the oral film becoming brittle. Polymer selection for oral films is dependent on compatibility with polymer and solvent[12]. Plasticizers help to improve the flow of polymer while increasing its strength. In fast dissolving oral films, plasticizers are used in 1-10% w/w of the dry polymer weight. It directly affects the folding endurance of the oral film. Plasticizers like

propylene glycol, glycerol, castor oil, and polyethylene glycol e.g. PEG 2000, PEG 4000, and PEG 6000 are used to formulate fast dissolving oral films.

Surfactants

Surfactants are the agents that help in solubilizing the strips easily to release the drug immediately. Sodium lauryl sulfate, Benzalkonium chloride, tweens, etc are some surfactants employed in fast dissolving oral film.

Saliva stimulating agent

It stimulates the salivary gland such that saliva is produced which acts as a vehicle for dissolving the oral film in the mouth. Acids like citric acid, tartaric acid, lactic acid, ascorbic acid, etc are used as saliva stimulating agents[13]. They are used in the concentration of 2-6% w/w of the strip.

Flavour

Flavors are the agents used to impart appreciable flavor to the formulation. Various flavoring agents including naturally extracted aromatic oils, resins, etc are used. They can be used individually or in combination where the concentration is dependent on the type and strength of the formulation and nature of API.

Colour

Colour enhances the appearance of the formulation. Titanium oxide, silicon dioxide, FD&C, etc are the agents used to impart the color in such formulation[14].

Sweetening agent

Sweetening agent as the name suggests itself, imparts a sweet taste to food and pharmaceuticals. The sweet taste of medicine play important role in the case of pediatric and geriatric patients. It increases the patient acceptance of the medication. There are two types of sweeteners used in pharmaceuticals, natural and synthetic. Synthetic sweeteners are several times sweeter as compared to natural sweeteners. But synthetic sweeteners are associated with many side effects which majorly have chances of cancer. Fast dissolving oral films usually include water-soluble sweeteners like glucose, ribose, maltose, sodium saccharin, aspartame, thaumatin, etc[15].

TECHNIQUES USE IN FILM PREPARATION[16-18]

1) Hot-melt Extrusion Method

Only thermostable drugs can be utilized in this procedure. In this procedure, a hot-melt extruder is used. In the hopper, the API and other excipients are mixed dry, heated to a high temperature, and then extruded as a molten mass. The mass is then utilized to shape and cut the film to the desired size. Drying takes place at a very low temperature. This procedure has the benefit of not requiring the use of any solvent.

2) Solvent Casting Method

The film is made by dissolving the polymer and API in a suitable solvent, stirring for a few hours with a magnetic stirrer, and then degassing the solution under a vacuum to eliminate any trapped air bubbles. The solution is poured into an appropriate casting mold, the film is dried by air or in an oven, and the film is gently removed.

3) Semisolid Casting Method

Water-soluble polymers are dissolved in water, and acid-insoluble polymers (Cellulose Acetate Phthalate, Cellulose Acetate Butyrate, etc.) are prepared in ammonium, and sodium hydroxide, as well as a plasticizer, is added to form a gel mass, which is then cast into a film using heat-controlled drums.

4) Roller method

In this approach, a solvent is employed to form a suspension or solution of the drug and polymer, which is usually water or a combination of water and alcohol. Specific rheological properties should be present in the suspension or solution. These are rolled with the help of a roller then dried and cut to the proper size with the use of prepared film.

5) Solid dispersion extrusion

This approach involves solid-state dispersion of one or more active substances in an inert carrier in the presence of amorphous hydrophilic polymers. The drug is dissolved in a suitable solvent and then integrated into polyethylene glycol at a temperature below 70°C. After that, solid dispersions are molded into films using dies.

EVALUATION PARAMETERS FOR FAST DISSOLVING ORAL FILMS[19-24]

1. Thickness test

The dosage accuracy of the drug in the film is determined by its thickness. It is measured with a micrometer screw gauge or a calibrated digital Vernier caliper at five distinct crucial places, with the mean value indicating the film's final thickness. The film thickness should be between 5 and 200 micrometers.

2. Tensile strength

It's the greatest tension that can be applied to a film point before the strip specimen breaks. Tensile strength is important in a film. Load failure refers to the weight at which the film breaks. The applied load at rupture is divided by the strip's cross-sectional area to determine tensile strength.

3. Percent elongation

When a film is stressed, it begins to stretch, which is referred to as a strain. Strain is calculated by dividing the film's distortion by its initial dimension. It is entirely dependent on the amount of plasticizer used. The percentage elongation of the film increases as the number of plasticizers increases.

$$\% \text{ elongation} = \text{Increase in length} / \text{original length} \times 100$$

4. Young's modulus

It is a measurement of the strip's rigidity. It's the proportion of applied stress overstrain in the elastic deformation zone. Hard and brittle films have high tensile strength and Young's modulus.

5. Tear resistance

It's the amount of force needed to tear the film. The load is applied at a relatively modest rate of 51 mm/min. The force is measured in Newtons or pounds.

6. Folding endurance

It indicates the film's brittleness. It can be done manually, depending on how many times the film has been folded without breaking or showing apparent cracks.

7. Morphology study

Scanning electron microscopy (SEM) is used to examine the morphology of the films at high magnification.

8. Contact angle

It gives information on wetting behavior, disintegration time, and oral film dissolving. This can be done at room temperature with the use of a goniometer. Double distilled water should be utilized for this purpose. A dry film is taken, and a drop of double distilled water is placed on the dry film's surface. Within 10 seconds after deposition, a digital camera captures images of water droplets.

9. Assay/drug content uniformity

This can be done using any of the standard assay methods defined in the standard pharmacopeia for the medicine in question. It is calculated by evaluating the drug content of each batch. The content uniformity limit is 85-115 percent.

10. In vitro disintegration test

When a film is exposed to water or saliva, it breaks or disintegrates at a certain point. Placing the film in the phosphate buffer is how this test is done. The disintegration time can also be measured using a disintegration device from the United States Pharmacopeia (USP). Disintegration time should be between 5 and 30 seconds.

11. In-vitro dissolution test

Dissolution is defined as the amount of drug substance that enters the solution per unit time under standard parameters of temperature, solvent content, and liquid/solid interface. For dissolution testing, any of the pharmacopeia's standard basket or paddle apparatus can be utilized. It's difficult to undertake a dissolving study of oral film using a paddle-type dissolution device since they can float above the dissolution liquid. The dissolving media chosen is determined by the sink circumstances and the drug's maximal dose. The temperature of the medium should be kept at 37 ± 0.5 ˚C and 50 rpm during the dissolving investigation.

12. Swelling property

Film swelling tests are carried out in a saliva-like solution. Each film sample is weighed and placed in a stainless steel wire mesh that has been preweighed. In a plastic container, the mesh containing the film sample is submerged in a 15ml medium. At a predetermined time interval, the weight of the film was increased until a steady weight was recorded. The degree of swelling was determined using the parameters wt-w0/w0, where wt is the film's weight at time t and w0 is the film's weight at time zero.

13. Stability studies

The formulation should be kept at 45°C and 75% relative humidity for 3 months. Triplicate samples are taken at three sampling intervals during the stability investigations, namely 0, 1, and 3 months, and films should be assessed for physical changes and drug content.

Patented Technology

Since fast dissolving oral film was untouched and very new to the pharma industry, many companies individually or in partnership with others had developed and patented the technologies with their uniqueness. There is a number of a patent registered and commercialized by companies of which a few are discussed below.

1) Pharmfilm

Pharmfilm® is a polymeric matrix made up of polyethylene oxide and hydroxypropylmethyl cellulose that is associated with quick dissolution and drug absorption. Pharmfilm has 80mg of drug loading capacity. This patented technology was developed by Monosol, which stands at the top in the oral film industry[25].

2) Rapid film

Rapidfilm is patent by teas Labtec. Rapidfilm® is a film-based delivery technology that has various advantages over traditional ODTs. Manufacturing is simpler and less expensive than ODT. Rapidfilms®, on the other hand, can be made quickly using a polymer solution and casting technique[26].

3) Smart film

Seoul Pharma created the SmartFilm® technology, an oral film with a high loading dose capacity of over 140 mg that can contain both hydrophilic and hydrophobic pharmaceuticals, as well as a unique taste-masking technology and an aqueous solution-based manufacturing process[27].

4) BEMA

BEMA was developed and patented for international rights by BioDelivery Sciences International. This drug delivery technique comprises a bioerodible polymer film that attaches to the oral mucosa quickly and has a backing layer that ensures the drug ingredient diffuses unidirectionally[28].

DISCUSSION

The recent global success and acceptance of rapid dissolving oral films demonstrate the necessity for effective taste-masked, "without water" medicinal formulations. Fast dissolving oral films, which are a logical progression of fast-dissolving drug delivery methods, offer significant benefits over traditional dosage forms and orally disintegrating tablets. Fast dissolving oral films have evolved as consumer-friendly dose forms as a result of their critical necessity in emergencies such as allergic reactions and high patient compliance.

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