



A Review on Fast Dissolving Oral Films: Recent Trend of Drug Delivery

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ABSTRACT

Orally fast dissolving films have been recently introduced in the market as a convenient and easy-to-use alternative to conventional dosage forms such as orally disintegrating tablets. For paediatric and geriatric patients, fast-dissolving drug delivery systems are an alternative to tablets, capsules, and syrups that quickly disintegrate and dissolve in saliva and can be easily swallowed without the use of water. Mouth dissolving buccal films are particularly useful for paediatric, geriatric, and mentally ill patients who have trouble swallowing conventional tablets. This approach improves the therapeutic efficiency of pharmaceutical actives by avoiding hepatic first pass metabolism, delivering drug molecules in a controlled manner, increasing absorption, and improving patient compliance. This review gives more details about the components used in ODF, the manufacturing processes, the evaluation tests, and the marketed products.

KEYWORDS: Fast dissolving oral films (FDOFs), Film forming polymers, solvent casting method, buccal mucosa, Patient compliance.

INTRODUCTION^[1-3]

Oral films are newer technologies in the production of oral disintegrating dosage forms. They are thin, elegant films composed of edible, water-soluble polymers in different sizes and shapes such as rectangles, squares, and discs. The stripes may be flexible or brittle, opaque, or transparent. They are intended to dissolve quickly on the tongue without the need for water. Fast dissolving films (FDFs) have a wide specific surface area for disintegration. The films minimize the risk/fear of choking, are easy to handle and administer, and provide easy-to-manufacture packaging, overcoming the short fails of oral fast disintegrating tablets. The low drug loading capacity and limited taste masking possibilities of these dosage forms are significant drawbacks. A fast disintegrating film is a thin film with a thickness of 1-10 mm and an area of 1-20 cm² of any geometry. Drugs should be incorporated up to a single dosage of around 30 mg. The quick dissolving of saliva is due to a special matrix composed of water-soluble polymers; it has a low tack for ease of handling and application. However, when wetting the wet tack and muco adhesiveness properties of system are designed to secure the film to the application site. The flexibility and strength of the films were chosen to facilitate the production process as well as processes such as rewinding, die cutting, and packaging. A fast dissolving film is put on the patient's tongue, which is mucosal tissue that is immediately wetted by saliva. The film hydrates quickly and adheres to the application site. It then quickly disintegrates and dissolves, releasing the drug for oral mucosal absorption or gastric absorption on swallowing.

The Benefits of FDOFs

- The large surface area promotes fast disintegration and dissolution in the mouth cavity.
- It is flexible and less fragile, it is easier to transport, store, and handle by the consumer.
- Ease of administration of mentally ill, disabled, and uncooperative patients.
- Accuracy in dosage administration.
- Excellent mouthfeel.
- Provides water-free treatment.
- Increased bioavailability, better absorption, and faster action.
- Improved patient compliance.
- Improve the product's life cycle.
- Excellent stability.



Fig.1: Oral film

Special Features of Oral Film

- Thin, attractive film
- Available in a variety of shapes
- Excellent mucoadhesion
- Fast disintegration and release

ADVANTAGES^[4-5]

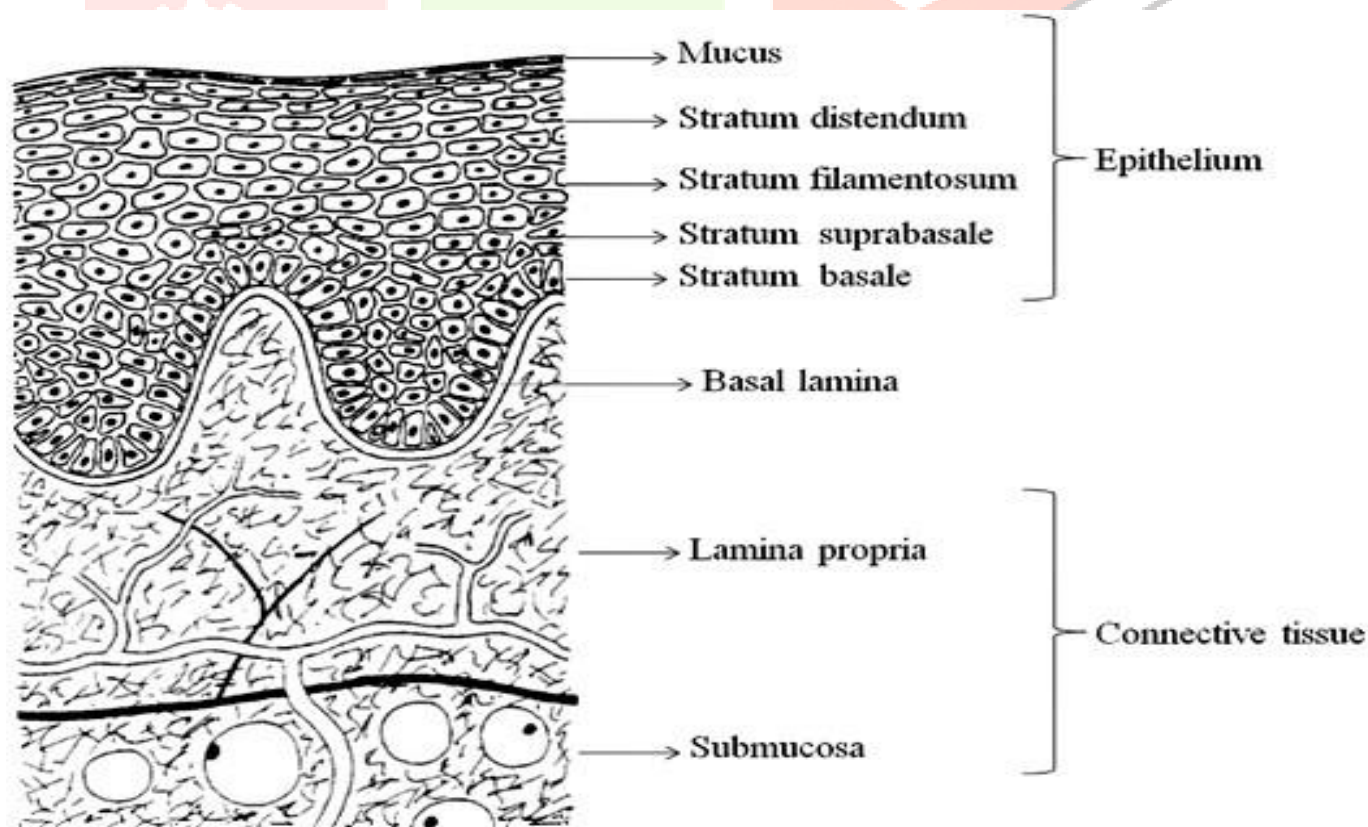
1. Easy transportation.
2. Ease of swallowing for Geriatric and paediatric patients.
3. Convenient and accurate dosing
4. There is no need for water for administration.
5. There is no risk of choking.
6. Rapid onset of action with improved bioavailability as a result of avoiding the hepatic first-pass effect and stability.

DISADVANTAGE^[6]

1. Film packing requires the use of specialized equipment.
2. Difficult to pack.
3. A high dose cannot be incorporated in an oral film.
4. Oral films that are moisture sensitive.
5. Eating and drinking can be prohibited.

Table 1: Comparison between fast dissolving films and tablet^[7-8]

| Oral dissolving Film | Oral disintegrating Tablet |
|---|---|
| Greater dissolution is due to the large surface area. | Because of the smaller surface area, there is less dissolution. |
| better durable than the orally disintegrating tablet. | As compared to oral films, they are less durable. |
| Increased patient compliance. | Patient compliance is less than film. |
| Only a low dosage can be incorporated. | A high dose can be incorporated. |
| There is no risk of choking. | It is fear of choking. |

Overview of Oral Mucosa^[9-11]**Fig.2: Schematic cross section through oral mucosa showing the epithelium, basal lamina and connective tissue**

The oral mucosa is constructed of an outermost layer of stratified squamous epithelium. Below this is a basement membrane, then a lamina propria, and finally the submucosa as the innermost layer. The epithelium is comparable to stratified squamous epithelia found throughout the body in that it has a mitotically active basal cell layer that advances through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the epithelium's surface. The buccal mucosa epithelium has 40-50 cell layers, whereas the sublingual epithelium has less. The epithelial cells increase in size and become flattened as they travel from the basal layers to the superficial layers. The surface epithelium of all covering and lining tissues in the body is supported by fibrous connective tissue. Because of its close packing and constant turnover of cells, the epithelium is well adapted to protect underlying tissues and organs from mechanical and chemical insult, whereas connective tissue, which consists of relatively few cells in a large matrix, provides mechanical support and nutrients to the epithelium. When the structure of the skin and oral mucosa is compared to the gastrointestinal tract, a major difference in epithelial organisation appears, which reflecting the different functions of these regions. The lining of the stomach, small and large intestines are made up of a simple epithelium with only a single layer of cells, which allows for easy absorption across the tissue. The skin, oral mucosa, and esophagus are covered by a stratified epithelium made up of many layers of cells that differentiate (or maturation) in different patterns between the deepest cell layer and the surface. Minor salivary glands in the esophagus can produce a secretion with a high bicarbonate concentration to neutralized refluxing stomach acid. In around three-quarters of adults, sebaceous glands can be found in the upper lip and buccal mucosa.

BUCCAL ABSORPTION^[12-13]

Buccal absorption leads to systemic or local action through the buccal mucosa.

Mechanism of Buccal Absorption

Buccal drug absorption occurs by passive diffusion of nonionized species via the epithelial intercellular spaces, which is primarily governed by a concentration gradient. The primary transport mechanism is the passive transport of non-ionic species across the lipid membrane of the buccal cavity. The buccal mucosa, like many other mucosal membranes, has been described as a lipoidal barrier to drug passage, and the more lipophilic the drug molecule, the more quickly it is absorbed. The kinetics of drug absorption in the buccal cavity could be adequately described by a first order rate process. There are a number of potential barriers to buccal drug absorption that have been identified. According to Dearden and Tomlison (1971), salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows :

$$- dm/ dt = Kc/ViVt$$

Where,

m - Mass of drug in mouth at time

K - Proportionality constant

c - Concentration of drug in the mouth at time

Vi - The volume of the solution put into mouth cavity and

Vt - Salivary secretion rate

FORMULATION CONSIDERATION^[14-20]

Orally Fast dissolving films have areas ranging from 5 to 20 cm² and incorporate the drug in the form of a matrix using a hydrophilic polymer. Fast dissolving oral films can contain up to 30 mg of active pharmaceutical ingredient (API) in addition to other excipients such as film forming polymers, plasticizers, surfactants, colourants, sweeteners, taste-masking agents, and so on. Plasticizer improves film workability, spreadability, and flexibility, reducing the glass transition temperature of polymers. The following is the general composition of an oral fast dissolving film:

Table 2: Formulation of film

| Sr. No | Composition of Film | Quantity |
|--------|--------------------------------------|----------|
| 1 | Active pharmaceutical ingredient | 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, Flavour, Colouring agent | Q.S |

i. Active Pharmaceutical Ingredient

The active pharmaceutical ingredient is usually present in the film composition at a concentration of 1-30% w/w. Because high drug doses are difficult to incorporate into a fast dissolving oral film, low dose active pharmaceutical ingredients should be used. Anti-histamine, anti-diarrheal, anti-depressant, vasodilators, anti-asthmatic, antiemetic, and other drugs should be used as fast dissolving oral films.

ii. Film forming polymer

Polymers are the most crucial components of a fast dissolving oral film, and polymer selection is one of the most important and essential parameters for the effective production of oral films due to their tensile strength, which varies depending on the type and quantity of polymer used. The amount of polymer used in the oral film determines the film's robustness. In general, 45 percent w/w polymer is used, depending on the overall weight of the dry film. The oral film is often made of hydrophilic polymers, which disintegrate quickly in the oral cavity as they come into contact with saliva. At the present, both natural and synthetic polymers are used in the production of fast dissolving oral films.

Ideal property of Film Forming Polymers:

- It should be non-toxic and non-irritant
- The polymer must be hydrophilic
- It should have excellent film-forming capacity
- The polymer should have good wetting and spreading ability.
- Polymer should be widely available and relatively inexpensive.
- Polymers should have such a low molecular weight.
- It should have a long enough shelf life.
- The polymer must be tasteless and colourless.
- It should not induce secondary infections in the oral mucosa, and it should have sufficient peel, shear, and tensile strengths.

Table 3: Most commonly used natural and synthetic polymers in Oral disintegrating film.

| Type of polymer | Example |
|-----------------|---|
| Natural | Starch, polymerized resin, pullulan, sodium alginate, Pectin, gelatin, and maltodextrins |
| Synthetic | Polyvinyl pyrrolidone, Polyvinyl alcohol, sodium carboxy methyl cellulose, hydroxy propyl cellulose and hydroxy propyl methyl cellulose |

iii. Plasticizer

It is a necessary component of oral films. The choice of plasticizer is depends upon its compatibility with the polymer as well as the form of solvent used in film casting. It increases the film's flexibility while decreasing its brittleness. By reducing the polymer's glass transition temperature, the strip properties of the plasticizer are significantly improved. They are used in concentrations ranging from 1 to 20% w/w of the dry polymer weight. Examples include Glycerol, propylene glycol, low molecular weight polyethylene glycols, citrate derivatives such as triacetin, acetyl citrate, phthalate derivatives such as dimethyl, diethyl, dibutyl derivatives, castor oil, etc.

iv. Sweetening agents^[21]

Sweetening agents have become an essential component in pharmaceutical agents intended to be disintegrated or dissolved in the oral cavity, and sweeteners are particularly important in paediatric formulations. Sweeteners are typically used in concentrations ranging from 3 to 6 % w/w, either individually or in combination. To increase the palatability of mouth dissolving formulations, both natural and artificial sweeteners are used. Sweeteners that are acceptable include :

A. Water soluble natural sweetener: Ribose, Xylose, glucose, sucrose, maltose, etc.

B. Water soluble artificial sweetener: Cyclamate salts, Calcium saccharin or Sodium salts, acesulfame-k, etc.

C. Dipeptide based sweetener: Aspartame.

D. Protein based sweeteners: Thaumatin I and II are two types of thaumatin. Fructose is sweeter than sorbitol and mannitol, and its sweetness is perceived faster in the mouth than sucrose and dextrose, so it is commonly used as a sweetener in oral films. Polyhydric alcohols such as sorbitol, mannitol, isomalt, and maltitol should be combined because they provide a good mouth-feel and a cooling sensation. Aspartame was used as a sweetening agent in the preparation of valdecocix oral films. Sucralose, Maltodextrin, and neotame were reported to be used to mask the bitter taste of diclofenac, ondansetron, and piroxicam fast dissolving films, respectively.

v. Saliva stimulating agent^[22]

Saliva stimulating agents are generally acidic in nature, promoting the disintegration of fast dissolving oral films by stimulating saliva production in the oral cavity. Some of the most commonly used saliva stimulating agents are citric acid, ascorbic acid, lactic acid, malic acid, and tartaric acid.

vi. Surfactants^[23]

Surfactants act as a solubilizing, dispersing, and wetting agent, allowing films to disintegrate quickly and release the incorporated drug. Surfactants also enhance the solubility of poorly soluble drugs soluble in fast-dissolving oral films. Surfactants that are commonly used include poloxamer 407, benzethonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, etc. Out of these most predominantly used surfactant is poloxamer 407 due to its numerous advantages.

vii. Stabilizing and thickening agents^[24]

In fast dissolving oral films, thickening and stabilizing agents are commonly used to enhance the consistency and viscosity of the dispersion or solution of the film preparation suspension or solution prior to casting. Natural gums such as xanthan gum, locust bean gum, carragenan, and cellulosic derivatives can be used as stabilizing and thickening agents in concentrations up to 5% w/w.

viii. Flavoring agents^[25]

Flavoring agents would be added to pharmaceutical oral preparations because flavours are the ultimate goal for the patients when selecting preparations. It might also be an important factor in sale of products. There is both natural and artificial flavour used. The amount of flavour required to mask the taste is determined by the flavour type and its strength. Flavours can be incorporated to formulation at a volume of up to 10% w/w. Flavoring agents can be selected from a variety of synthetic flavour oils, oleo resins, and extracts derived from different parts of plants such as leaves, fruits, and flowers. Flavouring agent can be used individually or in combination. Cinnamon oil, Peppermint oil, Spearmint oil, oil of nutmeg are examples of flavor oils while

cocoa, vanilla, coffee, chocolate, and citrus are fruity flavors and pineapple, apple, cherry, raspberry, are few examples of fruit essence type

ix. Cooling agents

Cooling agents, such as monomethyl succinate, can be added to enhance the mouth feel and flavour strength of the product. Some cooling agents, such as WS3, WS23, and Utracoll II, can be used in combination with flavours.

x. Colouring agents

Colouring agent is additives that add colour to a formulation. The colouring agents are chosen based on the flavour. The oral film contains FD&C-approved colouring agents. Titanium dioxide is the most commonly used colouring agent in fast-dissolving oral films and other pharmaceutical preparations. Colouring agent should not be used in concentrations greater than 1% w/w.

PROPERTIES OF ORAL FILMS^[26-27]

Table 4: Properties of the oral films

| PROPERTY | FLASH RELEASE | MUCOADHESIVE MELT RELEASE | MUCOADHESIVE SUSTAINED RELEASE |
|-------------------------|-------------------------------------|--|---|
| Area (cm ²) | 2-8 | 2-7 | 2-4 |
| Thickness (µm) | 20-70 | 50-500 | 50-250 |
| Structure | Film single layer | Single or multilayer system | Multilayer system |
| Excipients | Soluble, highly hydrophilic polymer | Soluble, hydrophilic polymer | Low/non soluble polymer |
| Drug phase | Solid solution | Solid solution/suspends drug particle | Suspension or solid solution |
| Application | Tongue (upper plate) | Gingival or buccal region | Gingival (or other region of oral cavity) |
| Dissolution | Maximum sixty second | Disintegration in few minutes, forming gel | Maximum 8-10 hrs |
| Site of action | Systemic or local | Systemic or local | Systemic or local |

METHOD OF PREPARATION OF MOUTH DISSOLVING FILMS^[28-37]

The Mouth Dissolving film can be manufactured using one or a combination of the following processes:

1. solvent casting method

Ingredients that are water soluble are dissolved in water.



Drug and other ingredients are dissolved in a suitable solvent to form a clear viscous solution.



Both solutions are mixed.



degass under vacuume



The resulting solution casted as a film.

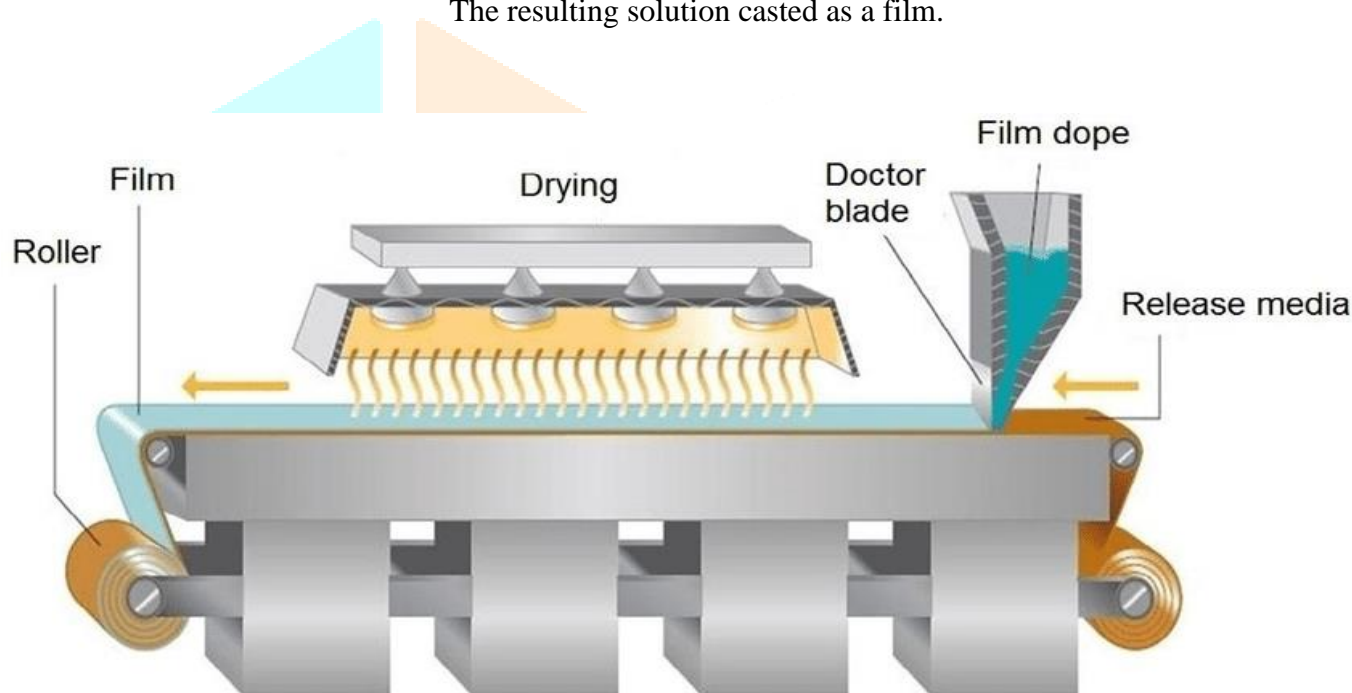


Fig.3: Solvent casting film system

Advantage:

- The film have great uniformity of thickness and better clarity than extrusion.
- Films have fine gloss & freedom from a defect such a die liners.
- Films have a lot of flexibility & good physical properties.

Disadvantage:

- The polymer must be soluble in volatile solvent or water.
- The stable solution with reasonable minimum solid content.

2. Hot melt extrusion

In solid form, the drug is mixed with carriers.



The mixture is melted by an extruder equipped with heaters.



Finally, the dies shape the melting mixture into films.

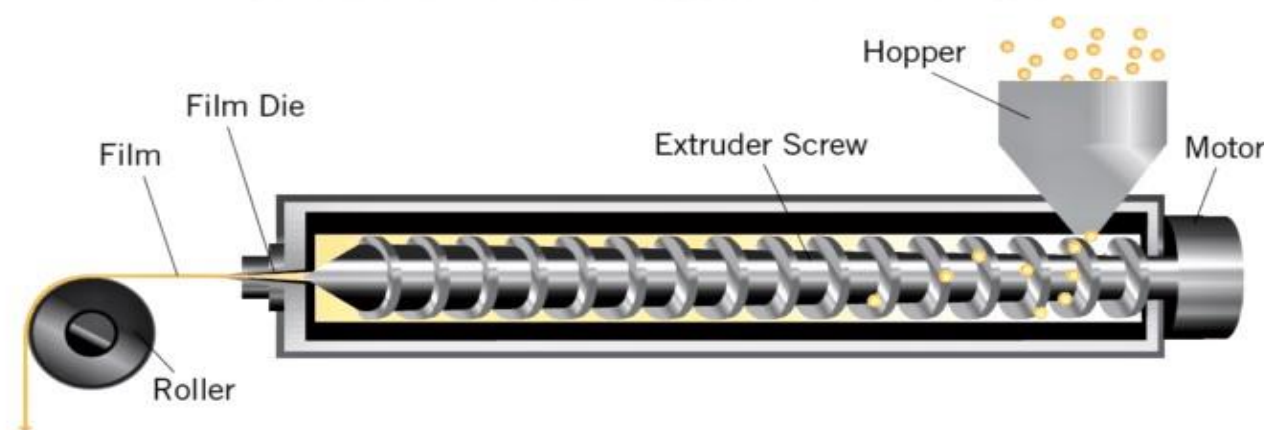


Fig.4: Hot melt extrusion process

Advantage:

- Fewer operation units
- Better content uniformity
- An anhydrous process

3. Semi solid casting

A solution of a water-soluble film-forming polymer is prepared.



The resulting solution is mixed with an acid-insoluble polymer.



An appropriate quantity of plasticizer is applied to the gel mass is obtained.



Finally, using heat-controlled drums, the gel is cast into the films or ribbons.

4. Solid dispersion extrusion

Drug is dissolved in a suitable liquid solvent or solvents



The solution is incorporated into the melt of Polyethylene glycol obtained below 70°C



Finally the solid dispersions are shaped into the films by using dies

5. Rolling method

Prepare a pre-mix of a film-forming polymer, a polar solvent, and other ingredients except a drug.



Premix can be added to the master batch feed tank.



It is fed to either or both of the first and second mixers through a first metering pump and control valve. Add the appropriate amount of drug to the desired mixer.



Blend the drug with the master batch premix to give a uniform matrix. A specific amount of uniform matrix is then fed to the pan through the second metering pump.



Finally, the film is forced on the substrate and carried away via the support roller.



Then the wet film is dried using controlled bottom drying.

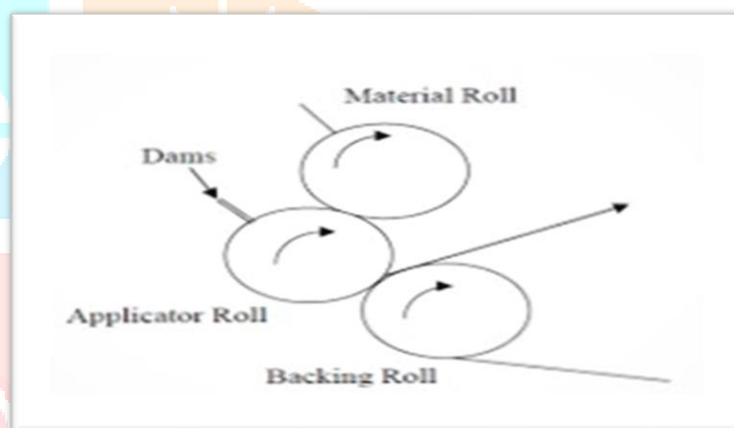


Fig.5: Three roller coating film forming unit

EVALUATION

The fast disintegrating oral films are evaluated for the following parameters

1. Weigh variation of Films^[38]

On an analytical balance, mouths dissolving oral films were weighted, and the average weight for each film was calculated. It is desirable for films to have a nearly constant weight. It is helpful for ensuring that a film has the appropriate amount of excipients and API.

2. Visual inspection^[39]

The Colour, homogeneity, and transparency of a prepared orally disintegrated film can be evaluated visually.

3. Thickness Test^[40]

The thickness of the film was measured at five different places using a micrometer screw gauge, and an average of three values was calculated. This is essential to ensure uniformity in the thickness of the film, which is directly related to the accuracy of the dose in the film.

4. Folding Endurance^[40]

Folding endurance is measured by manually folding the same place of film repeatedly until it breaks. The folding endurance value is the number of times the film can be folded without breaking.

5. Wetting time^[41]

A circular paper is placed in the petridish to evaluate wetting time, and 6 ml of 0.1 % w/v amaranth dye solution is prepared and added to the petridish. The film strip (2x2 cm²) is placed on the surface of tissue paper. The wetting time is the time required for the dye to appear on the surface of the film.

6. Surface pH^[41]

The test film was placed in a Petri dish and moistened with 0.5 ml of distilled water for 30 sec. After putting the electrode of the pH meter into contact with the surface of the formulation and allowing for 1 minute of equilibration, the pH was measured. For each formulation, an average of three determinations was performed.

7. Disintegration time^[42]

The disintegration apparatus mentioned in official pharmacopeias is used to determine a film's disintegration time. The disintegration time of a film is normally a function of its composition, as it varies with formulation and generally ranges from 5 to 30 sec. The USP disintegration apparatus is commonly used for this test. There are no official guidelines for determining the disintegration time of orally fast disintegrating films.

There are two methods of determining film disintegration time:

- The slide frame method - Pouring a drop of distilled water onto the film clamped into slide frames placed on a petri dish. The time it takes for the film to dissolve is noted.
- Petri dish method - A film is placed in a petri dish with 2 mL of distilled water. The time it takes for the film to dissolve completely is referred to as the disintegrating time.

8. Dissolution test^[43]

Dissolution testing can be carried out using either a standard basket or paddle apparatus described in any of the pharmacopeias. The dissolution medium will be chosen based on the sink conditions and the highest dose of the API. Many times the dissolution test can be difficult due to the tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

9. Contact Angle^[44]

Contact angle measurements are performed at room temperature with a goniometer (AB Lorentz and Wetter, Germany). A drop of distilled water is placed on the surface of the dry film. Images of water droplets are captured by a digital camera within 10 seconds of their deposition. Image software is used to analyze the visual images in order to evaluate the contact angle.

10. Stability Testing^[51]

Stability is measured by storing the oral strip under controlled conditions of 25°C/60 % RH as well as 40°C/75 % over a 12-month duration in a stability chamber according to the ICH guideline. Various evaluation parameters such as thickness, morphological properties, tensile strength, moisture content, and dissolution behavior are evaluated during the storage process.

PACKAGING OF FAST DISSOLVING ORAL FILM^[45-49]

There are a lot of packaging options available for oral thin films; however, the packaging should be chosen carefully to ensure the product's integrity. The requirements for unit dose packaging, barcode labelling, the content of instructions for usage, child-resistant sealing, and senior friendly packaging are all criteria that must be considered during packing.

The packing materials chosen must have the following characteristics:

- They must be nontoxic
- They must be approved by the FDA.
- They must not react to the product.
- They must not impart taste and odour to the product.
- They must fulfil any required temperature resistance requirements.

Various type of packaging

1. Pouches made of foil, paper, or plastic:

- It provides tamper-resistant packing.
- It provides a high level of environmental protection. A flexible pouch is formed during the product filling operation by either vertical or horizontal forming, filling, and sealing equipment.

2. Single pouches or aluminium pouches:

A peelable pouch for “quick dissolve” soluble films with high barrier properties is a soluble drug delivery pouch. Using a two-structure combination provides for one side to be clear and the other to be a cost-effective foil lamination having zero gas and moisture transmission. The single dose pouch protects both the product and the dosage.

3. Multiple-unit blister card

The blister container is made up of two parts: the blister (plastic), which is the formed cavity that holds the product, and the lid stock (aluminium), which is the material that seals the blister. Heat softening is used to make the blister packaging, and the following method is used: Heating softens a thermoplastic resin sheet. A softened sheet is vacuum dried and placed in a countered mould. After cooling, the sheet is removed from the mould. Proceed to the filling machine packing station. The product is placed in a previously formed semi-rigid blister, which is then lidded with the heat sealable backing material.

APPLICATIONS OF FAST DISSOLVING FILM^[49-50]

1) Topical applications: The use of dissolving films to deliver active agents such as analgesics or antimicrobial agents for wound care and other topical conditions can be feasible.

2) Gastro retentive dosage systems: Dissolvable films, which contain water-soluble and poorly soluble molecules of various molecular weights in a film format, are being considered as dosage forms. The films' dissolution could be triggered by the gastrointestinal tract's pH or enzyme secretions, and they could be used to treat gastrointestinal disorders.

3) Diagnostic devices:

Dissolvable films can be loaded with sensitive reagents for controlled release when exposed to biological fluids, or they can be used to create isolation barriers for separating various agents to allow a timed reaction within a diagnostic device.

LIST OF MARKETED PRODUCT OF ORAL FILM^[5]

Table 5: Some Marketed Product of Oral Film

| Oral film | Active Ingredient | Manufacturer/ markeded | Category |
|------------------------------------|-------------------------|-------------------------------|----------------------|
| Klonopin Wafers | Clonazepam | Solvay pharmaceuticals | Antianxiety |
| Listerine cool mint pocket paks | Cool Mint | Pfizer | Mouth freshener |
| Benadryl | Diphenhydramine HCl | Pfizer | Antiallergic |
| Listerine | cool mint | Pfizer | Mouth freshener |
| Chloraseptic | Benzocaine/ Menthol | Prestige | Sore throat |
| Gas-X | Simethicone | Novartis | Anti Flatuating |
| Sudafed PE | Phenylephrine | Wolters Kluwer Health Inc. | Releiving Congestion |
| SupressR | Menthol | InnoZenR, Inc | Cough suppressants |
| Triaminic | Diphenhydramine HCl | Novartis | Anti allergic |
| Theraflu | Dextromethorphan HBR | Novartis | Cough suppressants |

CONCLUSION

Fast dissolving oral film is an advanced drug delivery system that has achieved worldwide popularity due to increased patient compliance, rapid onset of action, avoidance of first-pass metabolism, prevention of drug degradation in the Gastrointestinal tract, and improved biopharmaceutical properties. These are also very important in paediatric and geriatric patients who are unable to swallow conventional oral dosage forms, resulting in ineffective treatment. Due to its immediate action, this could be the most acceptable drug delivery system in the future for delivering drugs in emergency situations such as allergic reactions, asthma attacks, hypertension, and heart attacks, and etc.

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