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A Review on Fast Dissolving Oral Thin Films

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ABSTRACT:
Patient compliance is an integral part of pharmaceutical research for better and sustained drug delivery.
The oral delivery of drugs is the most ideal route of administration due to ease of administration which increases the patient compliance. Many patients especially geriatric and pediatric have difficulty to swallow tablet, capsule. Hence an alternative to these, Fast Dissolving Drug Delivery System (FDDDS) were developed. Oral fast dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which quickly disintegrate or dissolves on tongue or in buccal cavity. The acceptance of this ingenious dosage form is increasing day by day due to several comparative advantages of being cost-benefit, instant dissolving without water aid. It is an alternative platform for molecules that undergoes high first pass metabolism.
Index terms: Oral film, Fast Dissolving Drug Delivery System, patient compliance, first pass metabolism

I INTRODUCTION

Among various routes of drug delivery, oral route is the most convenient and achieve better patient compliance. Drug administered orally undergo rapid disintegration in the salivary fluids of the oral cavity in less than a minute and the absorption of drug takes place in the gastro-intestinal tract. Fast Dissolving Oral Thin Films has a property of quick disintegrating or dissolve on tongue or in buccal cavity within few seconds after coming in contact with saliva. Since the mucosa is highly supplied with blood, it provides episode of allergic attack or coughing for those who have an active life style. It is also useful when local actions are desired such as local anesthetics for toothache, oral ulcer, or teething

Merits

- The presence of an immense surface area promotes rapid disintegration as well as dissolution.
- Ease of administration.
- Improved patient compliance.
- Being flexible and handy, fast dissolving thin films provide ease during storage.
- Site specific and also has local action.
- Fast dissolving oral thin film has longer and improvised stability.
- It delivers a pleasant mouthfeel and taste of bitter drugs can be masked.
- No risk of choking.
- The oral bioavailability of drugs also gets enhanced in this dosage form because of lesser drug decomposition.
- First pass metabolism is decreased.

Demerits

- It is difficult to pack because special moisture-resistant packaging is required as fast dissolving thin films are sensitive to moisture.
- Not suitable for irritable drugs and for the drugs which are unstable at buccal pH
- Only the drug which undergoes passive diffusion can be administered by this route.
- Drugs with high dose cannot be incorporated into the film.
- After consumption of oral film, eating and drinking is restricted for sometimes.

Characteristics

- Thin and elegant film.
- Adequate taste/ A pleasant sensation in the mouth.
- Unobstructive
- Having lesser friability and appropriate mechanical capacity.

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A TYPICAL COMPOSITION OF FAST DISSOLVING ORAL THIN FILM

S.No	Ingredient	Percentageamount%
1	Drug(API)	1-30%
2	Polymer	Upto50%
3	Plasticizer	0-20%
4	Surfactant(SolubilityEnhancer)	q.s
5	Saliva stimulating agent	2-6%
6	Sweetening agent	3-6%
7	Flavoring agent	0-10%
8	Coloring agent	q.s
9	Stabilizer or Thickening agent	0-5%

II CLASSIFICATION

Fast dissolving oral thin films are divided into three subtypes based on their properties.
1.Flash release
2.Mucoadhesive melt release
3.Mucoadhesive sustained release

- **Flash release**

Thickness and area of the flesh release wafer are approximate 20-70µm and 2-8 cm2 respectively. Structurally, it is single-layered, contains hydrophilic polymers of high solubility and solid solution as drug phase. It takes not more than a minute for the strip to dissolve over the tongue, providing either local or systemic action.

- **Mucoadhesive melt release**

Mucoadhesive melt away wafer acquires around 2-7cm2 area and 50-500µm thickness. The system may be single or multi-layered, with suspended drug particle or solid solution as a drug phase. Polymers used are hydrophilic and highly soluble. The strip, when placed inside the mouth, dissolves in a short period and forms a gel. The activity site could be local or systemic.

- **Mucoadhesive sustained release**

Mucoadhesive and sustain release film has about 2-4 cm2 and 50-250µm of area and thickness respectively. It is a multi-layered system, comprising of non-soluble or slightly soluble polymers. The phase of a drug may be a solid solution or suspension. The strip dissolves in maximal 8-10 hours after placing over the buccal or gingival region, with systemic or local activity.

III SELECTION OF EXCIPIENTS

Generally Recognized as Safe (GRAS-listed) and accepted excipients are used in the formulation of fast oral dissolving films.

- **Strip forming polymers**

It is the most essential and major component of the oral films. In the preparation of oral films various types of polymers are used. In order to get the required film properties polymers can be used alone or in combination. Strip forming polymer is the important constituent of the oral films so at least 45% w/w of polymers should be added. The polymer should have sufficient peel, tensile and shear strengths. The stiffness of the strip depends on the amount of polymer and the type of polymer in the formulation. Since the primary use of all thin film oral dosage forms relies on their disintegration in the saliva of the oral cavity, the water soluble. Excipients or polymer must be water soluble with low molecular weight, less toxic, non-irritant and devoid of leachable impurities to prepare a thin water-soluble film formulation. It should have good wetting and spread ability property. The polymer should not be very expensive, should be readily available and have excellent film forming capacity.

- **Penetration enhancers**

Penetration enhancers are used to improve the penetration of the active moiety. They should be non-irritant and have reversible effect. There are various chemicals to enhance the penetration that includes fatty acids (such as oleic acid), surfactants (such as tween), terpenes (like eucalyptus) and

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solvents (like ethanol). Others include azone, bile salts, currently chitosan, its derivatives, and polymers with the property of mucoadhesion.

- **Plasticizers**

Plasticizers helps to improve the flexibility of the film and also reduce the glass transition temperature of the polymer due to which the brittleness of the film gets reduced. Plasticizers also enhance the tensile strength and lessen brittleness. The plasticizer used should be suitable with the polymer and the used solvent. Plasticizers also enhance the tensile strength of the polymers. Use of unsuitable or huge amount of plasticizer can cause film cracking; splitting and peeling of the film. Some plasticizers alter the rate of the drug absorption. It should give the permanent flexibility to the film. Plasticization takes place by two mechanisms: internal plasticization which requires chemical interaction of molecular groups of the polymer itself and external plasticization where, a physically active plasticizer is externally added. External plasticization does not require chemical interactions in the product and hence, it is the desired mechanism of plasticization.

- **Surfactant**

Surfactants are used as wetting or solubilizing or dispersing agent so that the films gets dissolve within seconds and release the active agent immediately. Several surfactants are used in oral film. One of the most important surfactant is poloxamer 407 which is used as solubilizing, wetting and dispersing agent.

- **Stabilizing and thickening agents**

To improve the consistency and viscosity of the film, the stabilizing and thickening agents are added. Natural gum, like carrageenan, xanthan gum, locust bean gum and cellulose derivative are loaded up to 5% w/w.

- **Sweeteners**

Carbohydrates of low molecular weight specially sucrose are most commonly used sweeteners. Sucrose being colourless does not impart any undesirable colour to the final formulation and very soluble in water. It is stable over the 4-8 pH range. It masks the taste of both bitter and salty drugs. Polyhydric alcohols such as mannitol and sorbitol also exhibit sweetening and suitable for diabetic patients. Only six artificial sweeteners are allowed for oral use within the European Union, the most widely used is sodium or calcium salts of saccharin. Both the salts exhibit high water solubility and are physically and chemically stable over wide pH range. Less widely used artificial sweeteners are aspartame, thaumatin, acesulfame potassium, neohesperidine and sodium cyclamate. Main disadvantage with artificial sweeteners is bitter or metallic after taste. A quite new sweetening agent is stevia powder in U.S. market. It is taken from the extract of the leaves of the plant Stevia rebaudian abertoni which is natural, safe and nontoxic. It is 30 times as sweet as sweet as sucrose and heat stable.

- **Flavoring Agents**

It is used from the oleo resins, synthetic flavor oils, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors are often used alone or in the combination. The amount of flavor added depends on the flavor type and its strength. Any flavor can be added such as essential oils or water soluble extracts of menthol, intense mints such as sweet mint, peppermint, wintergreen, spearmint, cinnamon, clove, sour fruit flavor such as orange, lemon or sweet confectionary flavors such as chocolate, vanillin or fruit essence like apple, pineapple, cherry, raspberry.

- **Coloring agents**

Colors of full ranges are available including FD & C colours, natural colouring agents, EU colours, and natural juice concentrates, pigments such as silicon dioxide, titanium oxide and zinc dioxide and custom pantone-matched colours. Colouring agents should not exceed 1% w/w concentration level.

IV MANUFACTURING METHODS

The methods for the preparation of fast dissolving oral thin films are

- Solvent casting method
- Semisolid casting method
- Holt melt extrusion method
- Solid dispersion extrusion method.
- Rolling method

Among this, the most commonly used industrial methods are solvent casting method and holt melt extrusion method.

- **Solvent casting method**

i. Preparation of casting solutions

Polymers were weighed and kept for swelling in distilled water overnight and dissolved (heated, if necessary). The drug, plasticizer and sweetening agent were made soluble in distilled water and added to the above mentioned polymer solution. Then it was mixed thoroughly to form a homogenous

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mixture. Using distilled water the volume was made to 10 ml. By applying vacuum entrapped air bubbles were removed.

ii. Preparation of fast-dissolving films

The casting solution (10 ml) was poured into glass molds and dried at 40°C in a vacuum oven to evaporate the solvent. Peeled the patches and cut into a square. The instrument used is shown in Figure below.

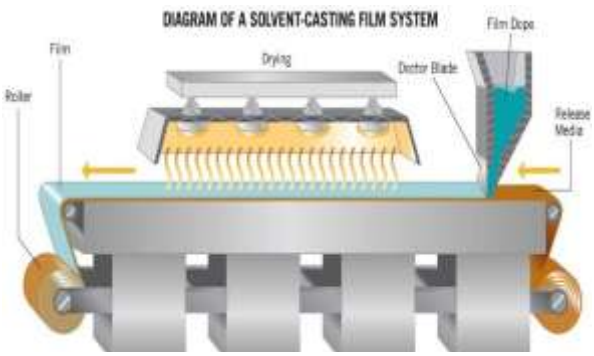

Figure: Solvent casting film instrument

- **Semisolid casting method**

In this method, first all the water soluble film forming polymers were solubilized. Then resulted solution was added to a solution of acid insoluble polymer. Then to obtain gel mass approximate amount of plasticizer was added. By using heat controlled drums the gel mass was casted into the films or ribbon. The thickness of film was about 0.015- 0.05 inches. The ratio of the acid insoluble polymers to film forming polymer should be 1:4.

- **Hot melt extrusion method**

i. Material preparation and blending

Weighed quantity of drug, saliva stimulating agent, and film former were dry mixed using a V-shell blender after passing through 30 mesh. The plasticizer and sweetener was incorporated slowly into a high-shear mixer containing the previously mixed blend with all excipients and blended for 10 min.

ii. Hot melt extrusion

The blends were melt-extruded using a co-rotating twin-screw extruder at 30–50 rpm over a temperature range of 100–110 °C. To release excess water vapor a degassing port was introduced in the last zone of the barrel. The presence of water vapour would produce unwanted bubbles in the films. Additionally, the film die was fixed with planned thickness. The blend was fed into the hopper, and the films

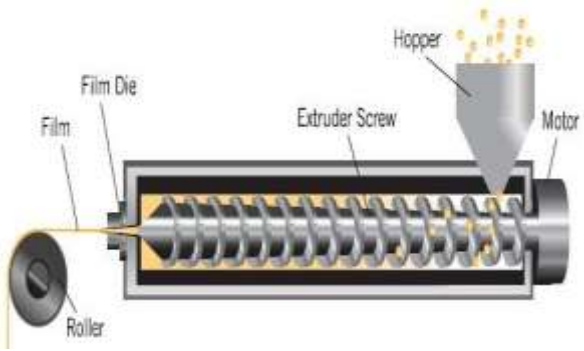

Figure: Holt melt extrusion instrument

iii. Solid dispersion extrusion

In this method, in a suspended carrier which was in a solid state, amorphous hydrophilic polymers, one or more active ingredients were dispersed. To obtain a solution, drug was dissolved in a suitable solvent. Then into the melt of suitable polymer below 70 °C without removing liquid solvent solution was added. Finally, solid dispersions were formed into films by a means of dies.

iv. Rolling method

In this method, film was formulated by preparation of premix. To the master batch feed tank, the pre-mix batch which includes film forming polymer, polar solvent and other ingredients except API were added. With the help of first metering pump and control valve a predetermined amount of the master batch was fed. To obtain a homogenized matrix the desired amount of drug was added into mixer and blended for a sufficient time. Through second metering pump a specific amount of matrix was fed into pan. The thickness of film was measured by metering roller. The film was finally formed on substrate and carried away by the support roller. Using controlled bottom drying the wet was dried.

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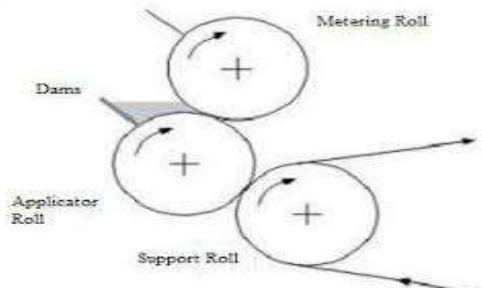

Figure: Rolling method

V EVALUATION PARAMETERS

Weight variation

Three films of 2 × 2 cm 2 size were cut randomly. Individually the films were weighed on electronic balance and the mean weight was calculated.

Thickness

The thickness of film is directly related to drug content uniformity so it is essential to find uniformity in the thickness of the film. It can be measured by calibrated digital Vernier Calipers. The thickness was measured at different spots of the films and average was taken.

Surface pH

This test was evaluated by placing the film in a Petri dish. Then it was moistened with 0.5 ml of 1% w/v solution of sodium lauryl sulphate in citro phosphate buffer pH 6.8 and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was taken.

Folding endurance

Folding endurance have been used to estimate the mechanical property of the film. It is done by folding the film repeatedly at the same place until it breaks. It is expressed in numbers. This also gives an indication of brittleness of the film.

Drug content

The film was dissolved in 10 mL of methanol and further diluted with 1% w/v solution of sodium lauryl sulphate in citro phosphate buffer pH 6.8 and solution was filtered and drug content was estimated at 242 nm using UV spectrophotometer.

Percent moisture loss

It is done to check the integrity of films at dry condition and hygroscopicity of a film. Three films of 2 × 2 cm 2 size were cut out and weighed accurately. Then the films were rested in a desiccator containing fused anhydrous calcium carbonate. After 3 days, the films were removed, weighed and percent moisture loss was calculated. Average PML of three films was calculated.

In vitro disintegration studies

The in vitro disintegration time of films were determined by the visual method. The film was placed in a glass Petri dish (6 cm in diameter) containing 6 ml of 1% w/v solution of sodium lauryl sulphate in citro phosphate buffer pH 6.8 at 37°C, with swirling every 10sec. The disintegration time was recorded as the time at which the film starts to break or disintegrate.

$$\% \text{ Moisture loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100\text{s}$$

Invitro dissolution studies

Determination of dissolution profile of films was carried out in a beaker containing 30 ml 1% w/v solution of sodium lauryl sulphate in citro phosphate buffer pH 6.8 at 37 ± 0.50 °C. Whole assembly was then placed on a shaker. Sample aliquot (5ml) was withdrawn at different time intervals and replaced with same fresh media.

Samples were filtered and diluted with 1% w/v solution of sodium lauryl sulphate in citro phosphate buffer pH 6.8 and analyzed by using UV spectrophotometer. The in vitro release data obtained were subjected to a zero order and first order kinetics to understand the release profile and release mechanism.

Stability studies

A stability study of optimized formulation was executed as per ICH guidelines. The single film was wrapped individually in butter paper followed by packing in aluminium foil and maintained at room temperature 25±25 ◌ C and 60±5% RH and placed in accelerated stability condition at 40±2◌ C and 75±5% RH for the period of 3 months. Changes in appearance, folding endurance, drug content, % drug release of the stored oral thin film were analyzed at a regular interval for 3months.

VI CONCLUSION

Fast dissolving oral films constitute an innovative dosage form and are one of the patient compliance, rapid release with improve bioavailability and are having great importance

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during the emergency cases such as hypertension, allergic reactions and asthmatic attacks whenever immediate onset of action was desired. Various research studies are published in the recent past which can be helpful in the industrialization of this unique and novel dosage form.

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