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FAST DISSOLVING ORO-DISPERSIBLE FILMS - A REVIEW

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ABSTRACT

Over the past few decades, there has been an increased curiosity to formulate the drug delivery system with advancement, improved safety and efficacy to patient. As new drug moiety is quite expensive the main aim is to develop a new drug delivery system with the same drug as it produce its maximum therapeutic effect over conventional. The fast dissolving oro-dispersible film is one of such drug delivery system which not only shows its popularity accepted by pediatric and geriatric patient but also many potential benefits are seen. It is a kind of drug delivery system which dissolves or disintegrates within a few seconds without the intake of water when placed in the oral cavity. It can be prepared by using various methods like solvent casting method, hot melt extrusion, semisolid casting, rolling method and solid dispersion extrusion. Present review provides an account of various formulation methods and their evaluation used in film formulations and applications of film. Today this drug delivery system is approved by FDA.

INTRODUCTION

For systemic effect the oral route is the most preferred route of administration. About 60% of all the formulations are solid dosage form. Tablet is the most desired dosage form due to ease of formulating, transportation and more patient compliance. Generally pediatric, geriatric, and bedridden patient experience difficulties in swallowing the conventional oral dosage form. To overcome this problem a new formulation was developed i.e. oral fast dissolving films [1]. Fast dissolving oral film is a new dosage form which consist of hydrophilic polymers, that quickly disintegrate or dissolve on tongue or in buccal cavity within a few seconds after coming in contact of saliva to release the drug without need of water or chewing unlike conventional dosage form. Since the mucosa is highly supplied with blood, it provides rapid absorption and immediate bioavailability of drugs. It is acceptable for the drugs that undergo high first pass metabolism [2, 3]. They are thin elegant films of various sizes and shapes like square, rectangle or disc. The strips may be opaque or transparent, flexible or brittle [4]. The first fast dissolving oral film was developed by major pharmaceutical company Pfizer who named it as Listerine pocket packs which are used as mouth freshening. Chloraseptic relief films were the first therapeutic oral thin films which were used to treat sore throat [5]. Fast dissolving oral film are convenient for patients such as pediatric, geriatric, bedridden, emetic patient, diarrhea, sudden 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 anaesthetic for toothache, oral ulcer, or teething [6]. The permeability of buccal mucosa is approximately 4-4,000 times greater than the skin, but less than the intestine. Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration. The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 μm layer. These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but are extremely sensitive to environmental moisture [7].

ADVANTAGES [8]

1. Ease of administration
2. Convenient in dosing.
3. No risk of choking.
4. Enhanced stability.
5. Improved patient compliance.
6. Taste of bitter drugs can be masked.
7. Site specific and also has local action.
8. Rapid drug release due to rapid disintegration and dissolution of films.
9. First pass metabolism is decreased.
10. Dose is accurate when compared to syrup.

DISADVANTAGES [9]

1. It is difficult to pack because packing requires special equipment.
2. Only small amount of drug can be incorporated.
3. Not suitable for irritable drugs and for the drugs which are unstable at buccal pH.
4. Longer preservation is difficult as it is hygroscopic in nature.
5. Only the drugs which undergoes passive diffusion can be administered by this route.
6. After consumption of oral film eating and drinking is restricted for sometimes.

SPECIAL FEATURES [7]

1. Thin and elegant film.
2. Available in various size and shapes.
3. It should easily adhere to the oral cavity.
4. Fast disintegration without water.
5. Unobstructive
6. Release should be rapid.

FORMULATION

Methods for manufacturing of fast dissolving oro-dispersible films were shown in figure 1

SOLVENT CASTING METHOD [10]

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

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 was shown in Figure 2.

SEMISOLID CASTING METHOD [11]: 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. 17.

HOT MELT EXTRUSION METHOD [12]

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 sweetner was incorporated slowly into a high-shear mixer containing the previously mixed blend with all excipients and blended for 10 min.

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 ℃. 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 were collected. The instrument used for hot melt extrusion were shown in Figure 3.

SOLID DISPERSION EXTRUSION [13] 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 ℃ without removing liquid solvent solution was added. Finally solid dispersions were formed into films by a means of dies.

ROLLING METHOD [14] 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.

Evaluation

FT-IR studies [15]

Fourier transform infrared spectroscopy (FT-IR) is a simple technique used to detect the changes with excipients - drug mixture. Reduction of the peak intensity combined with the appearance of new peaks or disappearance of an absorption peak gives a clear evidence for interactions between drug and excipients. For the FTIR studies, the samples was grounded gently with anhydrous potassium bromide and compressed to form pellet. The scanning range was 400-4000 cm-1.

Visual inspection [16]

The prepared films were evaluated visually for its clarity, stickiness and transparency. If the film gives satisfactory result it was taken for further evaluation or else they were discarded.

Drug Content [17] The film was cut and taken in a volumetric flask containing pH 6.8 phosphate buffer of 100 ml. For proper dissolution the medium was stirred on a magnetic stirrer for 6 hours. Using Whatmann filter paper the contents were filtered and the filtrate was analyzed by UV spectrophotometer. The experiments were performed for three films.

Transparency [18]

Transparency was evaluated by visual appearance of oral film and categorized in various levels such as best, good, medium, bad for transparency.

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 [19]. It is expressed in numbers. This also gives an indication of brittleness of the film [20].

Thickness [21]

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 micrometer screw gauge or calibrated digital vernier Calipers. The thickness was measured at different spots of the films and average was taken.

Surface pH [22]

Using water the film was slightly wetted. The pH was measured by introducing the electrode in touch with the surface of the oral film.

Swelling properties [23]

In this, the film was weighed and placed on a pre-weighed cover slip. It was placed in a Petri dish and added 50 ml phosphate buffer of 6.6 pH. After every 30 min, films were weighed by removing the cover slip. The difference in the weight

gives the increase in weight due to water absorption and swelling of film.

$$\text{Percent swelling} = \frac{\text{Xt} - \text{Xo}}{\text{Xo}} \times 100$$

Where,

Xt is the weight of the swollen film after time t

Xo is the initial weight of the film.

Weight variation [24]

From each film formulation three films of required size were cut randomly. Individually the films were weighed on electronic balance and the mean weight was calculated.

Percent moisture absorbance [25]

It is used to check the physical stability of the buccal films at high humid conditions. Three films were cut out and weighed accurately. Then the films were rested in a desiccator containing a saturated solution of aluminum chloride, 75% humidity was maintained inside the desiccator. After 3 days, the films were removed, weighed, and percent moisture absorbance was calculated. Average percent moisture absorbance of the films was calculated.

$$\text{Moisture absorbance} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

Percent moisture loss

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

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

***In vitro* disintegration studies** [26]

In this method, in a petridish 2ml of distilled water was taken and one film was placed on the surface of the water and the time required for the film to dissolve completely was measured.

***In vitro* dissolution studies** [27]

A film was placed in a beaker containing 20 ml of simulated salivary fluid (pH 6.8) as the dissolution medium maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (5 ml) of samples were collected at 5sec time intervals, and it was replaced with the same volume of fresh phosphate buffer. Samples were filtered, diluted and analyzed at 217 nm using ultraviolet-visible spectrophotometer. For all the samples three trials were carried out, and the average value was taken. The percentage of drug dissolved at various time intervals was calculated and plotted against time.

Mouth dissolving time [28]

It was determined by placing the film manually into a beaker which contains 50 ml of 7.4 pH phosphate buffer. Time required to dissolve the film was noted.

Organoleptic properties [7]

It is very important to focus on its organoleptic properties as the oral dissolving films intended to disintegrate quickly in oral cavity. Products which possess sweetness and flavor were mostly accepted by the people. For its psychophysical analysis special controlled human taste panels are used. Also taste sensors, specially designed equipment and drug release by changed pharmacopoeial methods are used for *invitro* method. Using electronic tongue measurements the difference between sweetness level in taste making formulation were found.

Stability studies [29]

The purpose of stability testing is to produce proof on however the standard of a drug substance or drug product varies with time below the influence of arrange of environmental factors such as light, temperature and humidity and also to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. It was carried out to assess the drug and formulation stability. It was done as per ICH guidelines Q1A (R2). The formulation was wrapped in aluminium pouch, sealed and stored with accelerated (temperature and relative humidity) condition for a period of two months. Films were evaluated after

intervals of 15 days for physical characteristics; mucoadhesive properties, in-vitro drug release, ex-vivo diffusion study.

Formulation of FDOFs

A typical composition of fast dissolving oro-dispersible films [30]

Active pharmaceutical ingredient : 25%
Plasticizer : 0-20%
Water soluble polymers : 40-50%
Fillers, colours, flavors, etc : 0-40%
Drug 25 %
- Water-soluble polymers 40 - 50 %
- Plasticizers 0 - 20 %
- Fillers, color, flavors etc. 0 - 40 %

INGREDIENTS

Strip forming polymers [31]

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 [32]

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

Plasticizers [33]

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. Glycerol, low molecular weight polyethylene glycols, propylene glycol, citrate derivatives such as castor oil, triethyl citrate, tributyl citrate and triacetin are some of the plasticizers commonly used.

Surfactant [34]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 solublizing, wetting and dispersing agent.

Stabilizing and thickening agents [35]

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

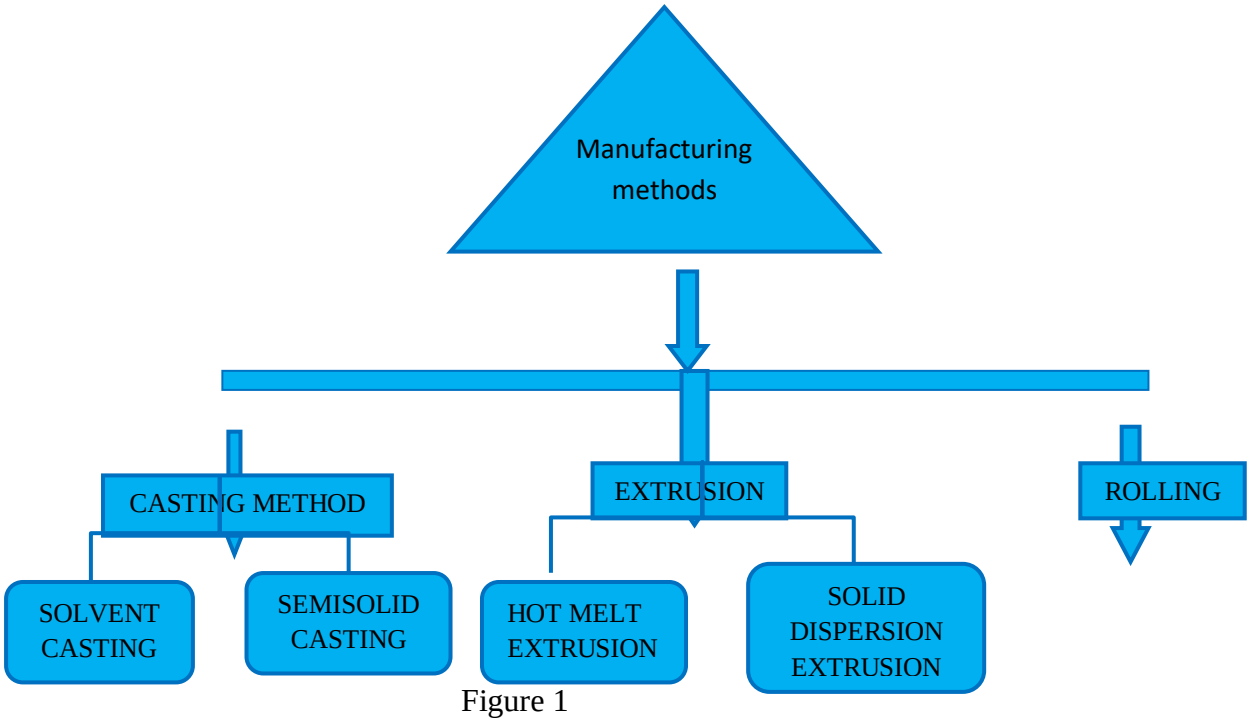

Figure 1

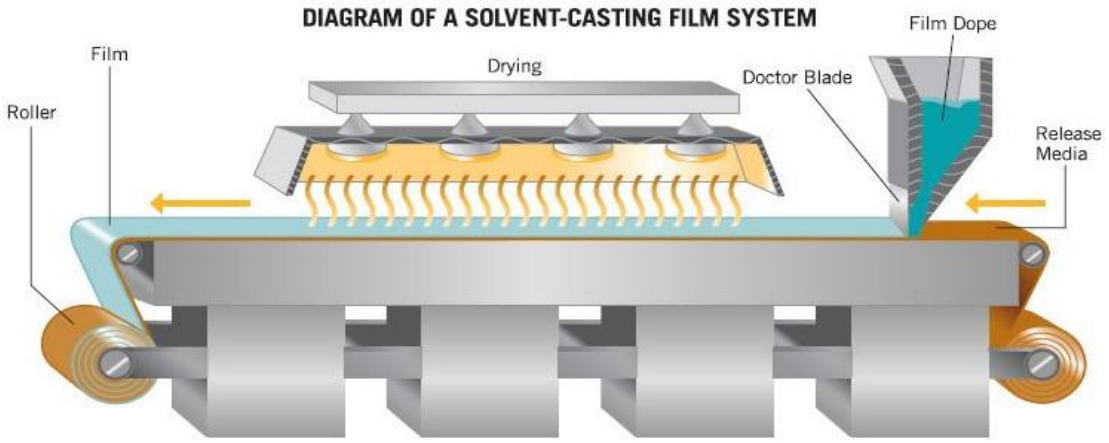

FIGURE: 2

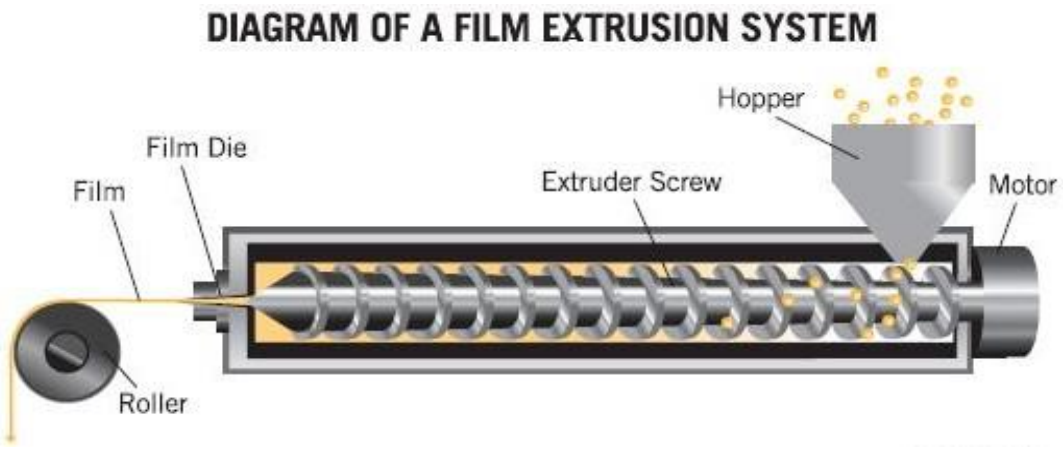

FIGURE: 3

Sweeteners [36]

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 [37]

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.

Colouring agents [38]

Colours 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.

PACKAGING

Packing considerations are important and critical for protection, storage and stability of dosage form. Packaging includes plastic pouches or foil paper, aluminum pouch, single pouch, barrier films and blister packaging with multiple units. For the drugs which are extremely moisture sensitive barrier films are most commonly used [19]. APR-Labtec has developed the rapid card which is proprietary and patented innovative packaging system. It is specifically designed for the rapid films. As like a credit card, the rapid card is exactly the same size and holds three rapid films on each side, allowing the patient to carry six single, packaged doses of his medication in his purse or wallet which is readily available. Every dose can be taken out individually. Another packing system Core-Peel® is developed by Amcor Flexibles and is gaining acceptance in the field of packaging of fast dissolving oro-dispersible films [30].

CONCLUSION

Fast dissolving oro-dispersible film is an innovative dosage form that is having great importance in emergency situations such as allergic reactions and asthmatics attacks and whenever immediate onset of action is desired. It could be a promising approach for the treatment by overcoming the drawbacks associated with conventional dosage forms. It guarantees patient compliance especially in case of pediatrics and geriatrics patients.

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