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Review Article

AN OVERVIEW : FORMULATION ASPECTS FOR MOUTH DISSOLVING FILMS

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An oral film delivery is emerging as an advanced alternative to the traditional oral method of drug administration. Active Pharmaceutical Ingredient: Various classes of drugs can be incorporated into ODFs e.g., anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc.Solvent casting is the most commonly used method for the preparation of ODFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor.Hot melt extrusion is a technique in which a mixture containing drug, polymer and excipients is extruded under high temperature to form a homogenous mass which is then coasted to form smooth films.Semi Solid Casting Methodis preferably adopted when acid insoluble polymers are to be used in the preparation of the films. Acid insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

Keywords: Fast Dissolving Oral Film, FDFs, Oral Film,Solvent Casting, Hot-melt Extrusion

INTRODUCTION

A fast dissolving oral film (FDOF) is defined as “an ultra-thin film containing active ingredient that dissolves or disintegrates in the saliva at a remarkably fast rate, within few seconds without the aid of water or chewing.An oral film delivery is emerging as an advanced alternative to the traditional oral method of drug administration. The oral film is a solid dosage form of drug administration that dissolves when administered. The oral film doesn’t need to be chewed or taken with water. Oral films contain active drugs that are designed for oral administration, allowing the drug to bypass the first-pass metabolism in the liver which leads to an increase in drug bioavailability.[1] Rapid or fast dissolving oral thin film is becoming an increasingly popular drug delivery system because of its wide and varied benefits. The oral film dissolves in few seconds when comes in contact with saliva, it doesn’t need water to swallow thus, it is considered best for children and elderly patients. Mouth dissolving films contain amorphous polymers which aid in the rapid dissolution of the drugs. Above points lead to improvement in patient compliance and inspire pharmaceutical manufacture to invest their money in switching from the former products in markets to FDFs [1,2]. The pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill is supposed to be swallowed intact or chewed to deliver a precise dose of medication to the patient. The pills, tablets, and capsules have the quality to retain their shapes under moderate pressure. Some patients,

especially geriatric and pediatric groups face difficulty in swallowing solid dosage forms and have the risk of choking. To comfort such patients, a variety of fast-dissolving drug delivery modes have been developed. Fast dissolving drug delivery systems are generally manufactured by a variety of technologies, which are direct compression, wet granulation and freeze drying. Some make use of different disintegrating mechanisms, such as high levels of disintegrating or effervescent agents, which cause the dosages to disintegrate rapidly in the mouth. The oral route of administration still continues to be widely used accepted route, contributing to 50 - 60% of total drug formulations because of ease of administration, self-medication, and pain avoidance as compared to parenteral mode[3]. Most commonly elderly patients experience problems in swallowing solid dosage forms.

Oral administration of conventional tablet poses problems, when a patient is mentally ill, developmentally disabled and in nausea. In some cases, motion sickness, sudden episodes of allergic attack or coughing and unavailability of water, poses problem in swallowing. To avoid such discomforts while having medication pharmaceutical technologists have developed several mouth dissolving drug delivery systems. Normally the films are soluble in water at room temperature and break up in 30 sec and vanish in a minute. As faster the drug goes into the solution, quicker its absorption and onset of clinical effect occurs. By altering the condition and formulation factors, it is possible to slow down or speed up dissolving rate in the mouth just by altering the formulation factors and conditions. The mouth dissolving films-contain active ingredients, flavors, sweeteners and other ingredients, these materials are released as the film dissolves.

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with saliva without chewing and no need of water for administration[4]. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin. FDOFs are useful in patients such as paediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing FDOFs are prepared using hydrophilic polymer that rapidly dissolves on the buccal cavity, delivering the drug to the systemic circulation via buccal mucosa. The fast dissolving drug delivery system are specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability.

Classification of Oral Films:

There are 3 types of oral films, they are:

a.Flash release/Fast dissolving films (placed on the tongue)

b.Mucoadhesive melt away films (gingival or buccal region)

c.Mucoadhesive sustained release films[5] (adhere to the buccal mucosa) (A.R Patel et al., 2010).

Special Features of Mouth Dissolving Films

1. Thin elegant film
2. Unconstructive
3. Available in various size and shapes
4. Fast disintegration
5. Rapid release
6. Give a pleasant mouth feel.
7. Have an acceptable taste.
8. Should not leave residues in mouth.

Categories of fast dissolving technology:

Fast-dissolve technologies can divide into 3 broad groups:

- Lyophilized systems
- Compressed tablet-based types
- Oral thin films

Lyophilized systems: This technology involves taking a suspension or solution of drug with other structural excipients, by using mould or blister pack, which forms tablet-shaped units.

Compressed tablet based-systems: The standard tablet technology by direct compression of excipients is used to produce this system. The tablet technologies have different levels of hardness and friability depending on method of manufacturing [6].

Oral Thin Films: It is also called as oral wafers. Form the past few years the oral thin films are evolved in confection and oral care markets in the form of breath strips.

Advantages of orally FDFs:

- ODFs can be administered without water, anywhere& anytime.
- Larger superficial area (LSA) films aid in rapid disintegration as well as in dissolution of the bodies oral cavity.
- Promoting mouth-freshening property. [7].

Disadvantage

Drugs that are required in high doses made difficult formulate into thin films. For instance, Rifampin (600mg), Ethambutol (1000mg). (BhupinderBhyan et al., 2011).

- Thermal process of drying affect drug & polymer stability
- Require packing(special) for products stability & safety.

Formulation Aspects for Mouth Dissolving Films:

Active Pharmaceutical Ingredient: Various classes of drugs can be incorporated into ODFs e.g., anti-histamine, anti-diarrheal, anti-depressants, vasodilators, anti-asthmatic, anti-emetic, etc. Dimenhydrinate can also be incorporated into ODFs for taste masking. Common examples of drugs incorporated into ODFs are salbutamol sulfate, rizatriptan benzoate, verapamil ondansetron,

dexamethasone, rofecoxib, cetirizine, pilocarpine, tianeptine sodium, indomethacin, etc.

Film Forming Polymer: Water-soluble polymers are used as film formers as they provide quick disintegration, good mouth feel, and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations. A variety of polymers are available for preparation of films of which pullulan, gelatin and hypromellose are most commonly used. Examples of watersoluble polymers include: Pullulan, Gelatin, guar gum, xanthan gum, Hydroxyl propyl methyl cellulose (HPMC), Modified starches, PVPK30, PVA etc. HPMC E3/E5/E6/E15.

Ideal Properties of the Polymers Used in the Oral Film:

1. Polymers should be nontoxic, non- irritant and non-bitter.
2. Polymers should be tasteless
3. It should be devoid of leachable impurities [8]
4. It should be inexpensive and readily available
5. It should not be an obstacle in the disintegration time
6. It should have good wetting and spreadibility property
7. It should exhibit sufficient peel, shear and tensile strength
8. It should not cause secondary infection in the oral cavity and should have sufficient shelf life.[4]

Plastisizers: In general, mechanical properties such as tensile strength and percent elongation are improved by adding plasticizer to the formulations. The concentration of plasticizer usually ranges from 0% to 20% w/w. Common examples of plasticizers are PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, etc.

Sweetening Agent: Sweeteners have become an important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. Some suitable sweeteners include: Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc.Water soluble artificial sweetener: sodium or calcium saccharin salts, acesulfame-K etc. Dipeptide based sweetener: aspartame.

Saliva Stimulating Agent:

Salivary stimulants are generally acidic in nature stimulating the production of saliva in buccal cavity, consequently, promoting the disintegrating of ODFs. Some commonly used saliva stimulating agents are citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid.

Surfactant:

Surfactants are used as solubilizing or wetting or dispersing agents as a result that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the

solubility of poorly soluble drugs in fast dissolving buccal films. E.g.: Polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and spans etc.

Flavor:

Flavors are needed to mask the bitter or nauseating taste of incorporated drug. Amount of flavor depends upon its nature and strength. Any US-FDA approved flavor can be used such as sweet, sour or mint flavor one of the research work verified that mint, licorice and sucralose mixture flavors appropriately mask the bitter taste of diclofenac sodium. Electronic tongues are used to discriminate the effect of various taste masking agents (TMAs)

Colouring Agent:

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in oral strips when some of the formulation ingredients or drugs are present in insoluble or suspension form[9] .

Method of Preparation of Fast Dissolving Film:

One or a combination of the following processes can be used to manufacture the Mouth dissolving film:

1. Solvent casting
2. Hot-melt extrusion
3. Semisolid casting
4. Solid dispersion extrusion
5. Rolling

Solvent Casting Method:

Solvent casting is the most commonly used method for the preparation of ODFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor. Then, the prepared solution is poured onto petri plate and the solvent is allowed to dry by exposing it to high temperature in order to attain good quality films. An orodispersible film of tianeptine sodium was successfully prepared through solvent casting technique using different grades of Lycoat and HPMC. In solvent casting technique, film forming polymer is usually soaked in an appropriate solvent for overnight. The type of API, which has to be incorporated in ODF, governs the selection of a suitable solvent depending on critical physico- chemical properties of API such as melting point, shear sensitivity and polymorphic form. Compatibility of drug with solvent and other excipients are also brought under consideration before finalizing a formulation. During formulation, entrapment of air bubbles can hinder the uniformity of prepared films. Thus, deaeration of the mixture is carried out with the help of a vacuum pump. Orodispersible film formulation of mosapride was also successfully prepared by using solvent casting method. Viscosity of the solution to be poured is an imperative aspect in casting method. The concentration of pullulan varying

from 2% to 8% results into low viscosity solution, as a result, enabling easy casting of films. Fast disintegrating films of anastrozole were also effectively prepared with the help of solvent casting method employing HPMC (E5) and polyvinyl alcohol (PVA) [6,10] .

Hot Melt Extrusion:

Hot melt extrusion is a technique in which a mixture containing drug, polymer and excipients is extruded under high temperature to form a homogenous mass which is then coasted to form smooth films. This is a solvent free process; however, the processing of thermolabile substances is a major drawback of this process due to the use of high temperature during extrusion.

Semi Solid Casting Method:

This method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films. Acid insoluble polymers used to prepare films include: cellulose acetate phthalate, cellulose acetate butyrate. Acid insoluble polymer and film forming polymer should be used in the ratio of 1:4.

Anatomical & Physiological Features of The Oral Cavity:

It was explained by the surface of the oral mucosa which was shown clearly in Fig1 1. And overall it is about 100cm^2 . It has the following parts like

- Buccal epithelium
- Basement membrane
- Sub mucosal membrane which contains nerves & blood vessels
- contains bone or muscle.

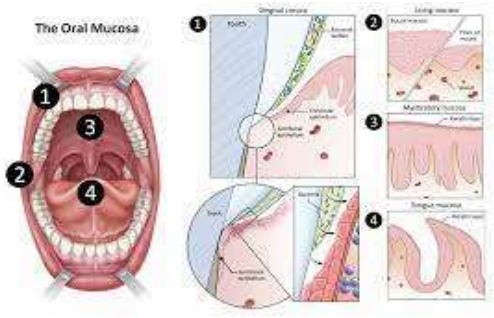

Figure 1: Oral Mucosa

Formulation considerations:

Formulation considerations are important factors affecting the mechanical properties of films such as, shifting the glass transition temperature to lower temperature. (Gerad J Tortora et al.,). Formulation of ODFs involves the intricate application of aesthetic and performance characteristics such as taste masking [9,10], fast dissolving, physical appearance, mouth-feel etc. The area of drug loaded FDF should be between 1-20 cm^2 [11]. The drug can be loaded up to a single dose of 30mg. (J. Aggarwal and G. Singh et al.,2011

Table 1: Composition of FDOFs

S. No.	Particulars	% value upto
1	Drugs (API's)	05- 30% w/w
2	Polymer (Water Soluble)	45% w/w
3	Sweetening agents	3- 6% w/w
4	Plasticizers	0-20% w/w
5	Saliva Stimulating Agents	2-6% w/w
6	Stabilizing agents	0.01-0.1% w/w
7	Surfactant	q.s.
8	Fillers	q.s.
9	Colours	q.s.
10	Flavouring agents	q.s.

CONCLUSION:

Solvent casting is the most commonly used method for the preparation of ODFs using water soluble excipients, polymers and drug which are dissolved in de-ionized water; consequently, a homogenous mixture is obtained by applying high shear forces generated by a shear processor. Hot melt extrusion is a technique in which a mixture containing drug, polymer and excipients is extruded under high temperature to form a homogenous mass which is then coasted to form smooth films.Semi Solid Casting Method is preferably adopted when acid insoluble polymers are to be used in the preparation of the films.

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