International Journal of Research in Pharmacy and Allied Science (IJRPAS)
Published by Ideal Publication
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FAST DISSOLVING ORAL THIN FILMS: A NOVEL APPROACH FOR DRUG DELIVERY

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Article History
Received: 20/12/2022
Revised: 24/12/2022
Accepted: 29/12/2022
Published: 01/01/2023

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Abstract: Oral route is the most preferred route of administration for the systemic effect. Approximately, 60% of all the formulations are solid dosage form, because of its low-cost and ease of administration increases the patient compliance. FDDDS were developed for those patients who have difficulty to swallow the tablets and hard gelatine capsules especially geriatric and paediatric patients. These dosage form is an alternative to tablet, capsule and syrups. Mouth dissolving films are more acceptable and accurate oral dosage form which bypass hepatic first-pass metabolism and provide therapeutic response by increasing bioavailability. This technology has been used for local action and quick release of the drug. It is relatively a new dosage form in which thin film is prepared by using water soluble polymers, which is rapidly disintegrate or dissolves on tongue or in the oral cavity. The present study gives aknowledge of different formulations, methods of preparation and quality control of the fast-dissolving oral thin films.

Keywords: fast dissolving oral thin films, Patient compliance, First pass metabolism, hydrophilic polymers.

INTRODUCTION

Among the various routes, the oral route is the most acceptable for the patientsdue to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Tablet is the most preferred dosage form due to ease of transportation, manufacturing and more patient compliance.[1,2]Generally geriatric, paediatric, bedridden, diarrhoea, sudden episode of allergic attack, coughing, emetics, emergency(cardiac), patient experience have difficulties in swallowing the conventional oral dosage form.To overcome this problem a novel formulation was developed i.e., oral fast dissolving films. These are also useful for local effect such as local anaesthetic for toothache, oral ulcers, cold sores or coughing.[3] It improve the efficacy of APIs compared to fast dissolving tablets, by dissolving in the oral cavity after the contact with less saliva without chewing and no need of water for administration.[1,4]The delivery system consists of a thin film, which is placed on the patient's tongue or mucosaltissue, instantly wet by saliva; the film rapidly dissolves. Then, it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption.[2,5,6]It improve the efficacy of API within minute dissolved in oral cavity after contact with saliva without chewing and no need of water for administration. Fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moisture environment.[2,7]The fast-dissolving drug delivery system is specially designed for the drugs which have extensive first pass metabolism and have low dose, for the enhancement of bioavailability.

Mouth dissolving films is an ultra-thin film that employs a hydrophilic polymer that rapidly hydrates or adheres when placed on the tongue or in the oral cavity. These films disintegrate or dissolve within seconds to release the active agent without drinking and chewing. There is no need of water for administration of these dosage form. As the oral mucosa is highly enriched with blood supply, it provides quick absorption and instant bioavailability of drugs. The instant bioavailability results from bypassing first pass metabolism. So, they are generally designed for the drugs having high first pass metabolism for achieving better bioavailability. The oral thin-film technology is still in the beginning stages and has bright future ahead because of patient compliance.

There are some Factors which are taken into Consideration

- Drug Lipophilicity.
- Solubility
- pH and pKa of saliva.
- Release of drug from the formulation.

Salient Feature of Fast Dissolving Drug Delivery System

- Ease of administration for patients who are mentally ill disabled and uncooperative.
- Require no water.
- Overcomes unacceptable taste of the drugs.
- Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Cost effective.

Types of Fast Dissolving Oral Film

There are three subtypes:

- Flash release.
- Mucoadhesive melt release.
- Mucoadhesive sustained release.

Advantages

- There is no need of water for administration.
- Large surface area of the film provides rapid disintegration and dissolution in the oral cavity.
- It should be flexible and light in weight.
- It is appropriate to all age group.
- Appropriate for patients who are ill or uncooperative.
- Avoiding the risk of choking
- Avoid first pass metabolism and provide quicker onset of action at lower doses.

Disadvantages

- High doses cannot be incorporated.
- Dose uniformity is a technical challenge.
- Hygroscopic in nature.
- Require special packaging for products.
- Stability and safety.

Ideal Characteristics of Suitable Drug Candidate

- The drug should have pleasant taste.
- The drug to be incorporated have low dose up to 40 mg.

- The drugs with smaller and moderate molecular weight are preferable.
- The drug should have good stability and solubility in water as well as in saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have the ability to permeate oral mucosal tissue.

Standard Composition of Fast Dissolving Oral Thin Film

It is a thin film having an area of 5-20 cm 2 containing drug. The drugs can be loaded up to a single dose of 30 mg. From the regulatory perspectives, all the excipients used in the formulation must be generally regarded as safe (i.e., GRAS-listed) and must be approved for use in oral pharmaceutical dosage forms. A typical formulation contains the following ingredients

- Active Pharmaceutical Ingredient
- Film Forming Polymer
- Plasticizer
- Sweetening Agent
- Saliva Stimulating Agent
- Flavouring Agent
- Colouring Agent

Table 1: concentration of compositions

o.	edients	centrations
	ve Pharmaceutical Ingredient	%
	Forming Polymer	5%
	ticizer	%
	etening Agent	́o
	va Stimulating Agent	́o
	ouring Agent	%
	uring Agent	́o

Active Pharmaceutical Ingredient:

A composition of the film contains 1-25% w/w of the drug. Variety of APIs can be delivered through fast dissolving films. Small dose molecules are the best candidates to be incorporated in OFDFs. Multivitamins upto 10% w/w of dry film weight was incorporated in the films with dissolution time of less than 60 seconds. It is always useful to have micronized API which will improve the texture of the film and

also for better dissolution and uniformity in the OFDF. Many APIs, which are potential candidates for OFDF technology, have bitter taste. This makes the formulation unpalatable especially for paediatric preparations. Thus, before incorporating the API in the OFDF, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation.

Film Forming Polymers:

Water-soluble polymers are used as film formers as they provide rapid 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. Watersoluble polymeric film adheres to the buccal mucosa and rapidly delivers medication into the systemic circulation. Various polymers are available for preparation of films of which pullulan, gelatine and Hypromellose are most commonly used. Generally, 45%w/w of polymer should be present in the total weight of dry film.

Table 2: Film Forming Polymers

Natural polymer	Synthetic polymer
Pullulan	Hydroxypropyl methyl cellulose
Xanthan gum	Polyvinyl pyrrolidone
Pectin	Polyvinyl alcohol
Starch gelatine	Carboxy methyl cellulose
Sodium alginate	Poly ethylene oxide
Maltodextrin	Hydroxypropyl cellulose
Polymerized rosin	Kollicoat

Ideal Property of Film Forming Polymers:

- It should be non-toxic and non-irritant
- Polymer must be hydrophilic
- It should have excellent film forming capacity
- It should have good wetting and spread ability property
- Polymer should be readily available & should not be very expensive.
- Polymer should have low molecular weight.
- It should have sufficient shelf-life.
- Polymer must be tasteless, colourless.
- It should not cause any secondary infection in oral mucosa.
- It should exhibit adequate peel, shear and tensile strengths.

Plasticizers:

It is an essential ingredient of the oral films. The selection of plasticizer depends upon its compatibility with the polymer and also the type of solvent employed in the casting of film. It improves the flexibility of the film and reduces the brittleness of the film. The strip properties of plasticizer are significantly improved by reducing the glass transition temperature of the polymer. They are used in the concentration of 1 – 20%w/w introduction Department of Pharmaceutics AACOP, Akkalkuwa. 12 of dry polymer weight. Examples include: Glycerol, propylene glycol, Low molecular weight polyethylene glycols, Citrate derivatives like triacetin, acetyl citrate, phthalate derivatives like dimethyl, diethyl, dibutyl derivatives, Castor oil etc.

Sweetening agents:

Sweeteners have become the important part of the formulation intended to be disintegrated or dissolved in the oral cavity. Generally, sweeteners are used in the concentration of 3-6% w/w. both natural and artificial sweeteners are used in the formulation of these fast-dissolving films. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth feel and cooling sensation. However, it should be noted that they use of natural sugars in such preparation need to be restricted in people who all are on diet or in the case of diabetic patents. Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations.

The first generation of the artificial sweeteners are

- Saccharin
- Cyclamate
- Aspartame

Saliva Stimulating agents:

The purpose of using the saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving stripes formulations. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. Examples are

- Citric acid
- Malic acid
- Lactic acid
- Ascorbic acid
- Tartaric acid

These agents are used along are in combination between 2-6 % w/w of the stripes.

Flavouring agents:

Preferably upto 10 % w/w flavours is added in the OFDF formulations. The acceptance of oral disintegrating or dissolving formulation by an individual is largely depends on the initial flavour quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. The geriatric population like mint or orange flavours like fruit punch, raspberry etc. it can be selected from synthetic flavour oils, oleoresins peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are the examples of flavour oils while vanilla, cocoa, coffee, chocolate, and citrus are fruity flavours. Apple, raspberry, cherry, pineapple are few examples of fruit Essence type.

Colouring agents:

FD&C approved colouring agents are used (not exceeding con centration levels of 1 percent; w/w) in the manufacturing of orally fast dissolving films. E.g., titanium dioxide.

METHODS OF PREPARATION OF FAST DISSOLING ORAL FILMS

One or combination of the following process can be used to manufacture the mouth dissolving films.

- Solvent casting method
- Semisolid casting method
- Hot melt extrusion method
- Solid dispersion extrusion
- Rolling method

Solvent Casting Method:

In this method water soluble polymer and plasticizer are dissolved in the distilled water. The solution is stirred up for 2 hrs in the magnetic stirrer and kept aside to remove all the air bubbles entrapped. Then, the other excipients and API are separately dissolved and stirred well for time of 30 min, after stirring is done both the solutions are mixed together. Finally, the solution is casted on a suitable flat surface to form a film. The film is dried and carefully removed.

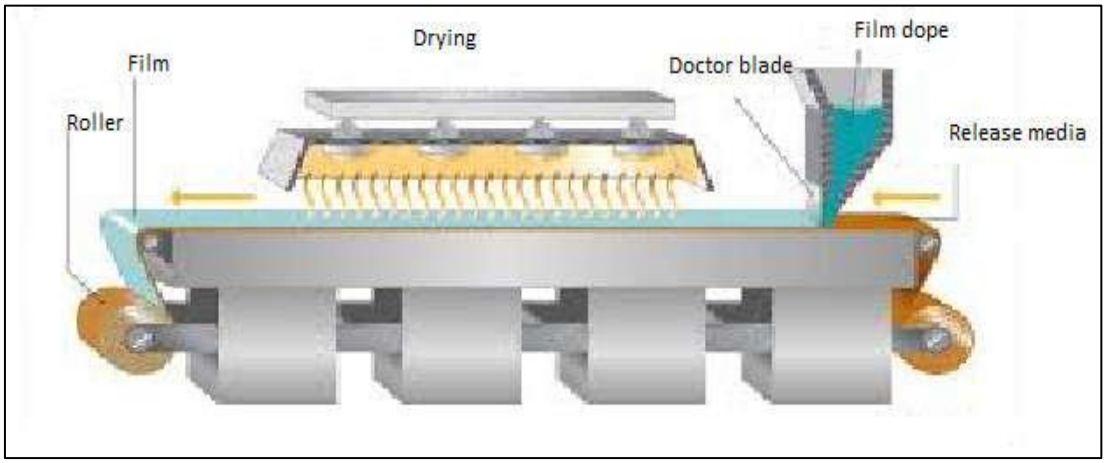

Fig 1: Diagram of Solvent Casting Film System

Advantage:

- Great uniformity of thickness and great clarity than extrusion.
- Films have fine gloss & freedom from defect such a die liner.
- Films have more flexibility & better physical properties.

Semisolid Casting Method:

In the semisolid casting method firstly a solution of film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymerwhich was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so toast a gel mass is obtained. Finally, the gel mass is casted into the films or ribbons using heat-controlled drums. The thickness of the film is about 0.15-0.5 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Both mixtures are mixed to form homogenous viscous solution degassed under vacuum. Bubble free solution is coated on non-treated casting film coated film is sent to aeration drying oven. Film is cutting into desired shape and size.

Hot Melt Extrusion:

In the hot melt extrusion method firstly, the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally, the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion method:

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

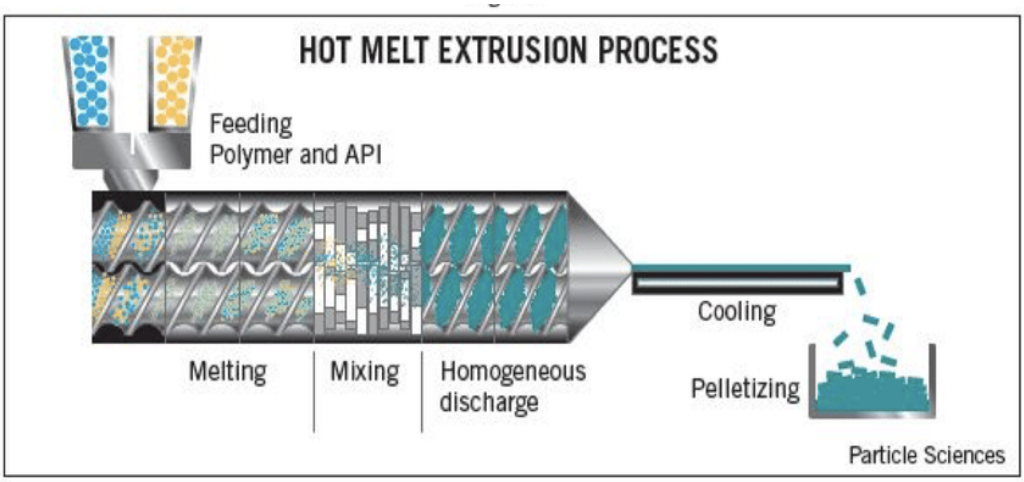

Fig 2: Diagram of Hot Melt Extrusion Method

Solid Dispersion Extrusion:

Solid dispersion refers to the dispersion of two or more active ingredients in an inert carrier in the presence of amorphous hydrophilic polymers in solid state. The API is dissolved in suitable solvent and incorporated into PEG. The drug and solvents are immiscible in nature. Solid dispersions are then shaped into films by means of dies.

Rolling Method:

In rolling method, a solution or suspension of drug with film forming polymer is prepared and subjected to the roller. The solution or suspension should have specific rheological consideration. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes. ble flat surface to form a film. The film is dried and carefully removed.

EVALUATION OF FAST-DISSOLVING ORAL FILMS

Prepared films are evaluated for following parameters.

1. Organoleptic Evaluation:

As the film disintegrates in the oral cavity, it should have acceptable organoleptic characteristics like colour, flavour and taste.

2. Weigh of Films:

Mouths dissolving oral films were weighed on analytical balance and average weight can be determined for each film. It is desirable that films should have nearly constant weight. It is useful fordetermine the proper amount of excipients and API.

3. Thickness of Films:

By using micrometer screw gauge, the thickness of the film was measured at five different places; an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

4. Folding Endurance:

To determine folding endurance, a strip of film is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Typical folding endurance for film is between 100-150.

5. Tensile Strength:

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by formula,

$$Tensile\ strength\ = \frac{load\ at\ failure\ X\ 100}{\text{strip thickness X strip width}}$$

6. Percent Elongation:

When stress is applied to a film sample it stretches and this is referred as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally, elongation of film increases as the plasticizer content increases.

It is calculated by formula,

$$\%\ Elongation = \frac{\text{Increase in length of strip X 100}}{\text{Initial length of strip}}$$

7. Surface pH:

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water 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 done.

8. In Vitro Disintegration Test:

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast-dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study Disintegration time. In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates.

9. Drug Content Uniformity:

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%.

10. In-Vitro Drug Release Study:

By this method cumulative drug release and cumulative percentage of drug retained were calculated. In-vitro drug dissolution was performed using USP paddle type apparatus. The studies were carried out at 37°C with stirring speed of 75 rpm in 500 ml phosphate buffer (pH 6.8). 5 ml of samples were withdrawn at predetermined time intervals of 3, 6, 9…, 30 min and replaced with the same volume of buffer. The samples were collected and the concentration was determined at appropriate wavelength using UV-visible spectrophotometer.

11. Stability Testing:

Stability measurement is done by storing the of oral strip were stored under controlled conditions of 25ºC/60% RH as well as 40°C/75% over a period of 3 months in stability chamber according to the ICH guideline. During storage period various evaluating parameter like thickness, morphological properties, tensile strength, water content and dissolution behaviour are checked.

CONCLUSION

The fast-dissolving oral thin films are considered as the novel work in the pharmaceutical field, this approach of delivery system is best suited for geriatric, paediatric and psychiatric patients who have difficulty in swallowing, so this approach exhibits less risk and improved patient compliance with higher safety. Since FDOF's bypasses the hepatic metabolism, its ease of administration and requires no water at the time of drug administration makes this delivery a unique one, and improves the therapeutic response significantly.

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