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Review Article

MOUTH DISSOLVING FILM AND THEIR PATENT: AN OVERVIEW

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ABSTRACT

Now days the researchers are focusing on the fast dissolving dosage form (FDDF's).The fast dissolving dosage forms includes the mouth dissolving tablets, mouth dissolving thin films .The alternative words used for these dosage forms are fast disintegrating, orodispersible, fast dissolving. The oral thin film technology (OTF's) is a dissolvable film technology have evolved from a purely confectionery novelty from a drug delivery platform. The OTH dosage form dissolves in the moth without need of water and within 10-15 seconds is the novelty of this dosage form. On the basis of this novelty many patents are available in the US country. Intraoral delivery is particularly beneficial to patients with special needs that are unable to tolerate traditional oral (entral/through GI track) administration due to nausea, vomiting or dysphasia. Many pharmaceutical companies focusing on this Oral thin film technology. Today, this film technology is approved by is approved by FDA.

Keywords: Oral Thin Film, Pullulan, Folding Endurance

INTRODUCTION

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms[1]. These films are made up of the water soluble polymer which when placed on the tongue instantly dissolves or disintegrate the medication without need of water. These films are suitable for the pediatric patients and avoids nausea, vomiting or dysphasia caused due to oral administration of traditional dosage forms[2].The evolution of thin film dosage forms are described in figure:1 form confectionary use to current pharmaceutical application[3].

TYPES OF MOUTH DISSOLVING FILM

A. Flash release film.
B. Flash Dispersible film.
C. Non-disintegrating mucoadhesive films.
D. Medium disintegrating mucoadhesive films.

Advantages[4]

a) No special training is required for the administration of dosage form.
b) No need of water, drug wet by saliva and instantly dissolves or disintegrates.
c) Availability of larger surface area for drug absorption.
d) Destructive acidic environment effect of stomach can be avoided
e) Site specific and rapid onset of action.
f) Drug enters systemic circulation with reduced hepatic first pass effect.

Disadvantage

a) Higher doses cannot be incorporated.
b) These dosage forms are moisture sensitive.

GENERAL PROPERTIES AND RELEASE MECHANISM

The Quick-Dis™ drug delivery system comprises a thin, printable, low-moisture, non-tacky film that is convenient for dosing, suitable for labeling, and flexible for easy packing, handling and application. These films are 1-10mm in thickness and having total surface area about 1-20 cm^2.These thin films when comes in contact with the saliva rapidly hydrates and breaks after softening release the medicaments. The typical disintegration time when comes in contact with the water is about 1-30 seconds[5].

PATENTS ON MOTH DISSOLVING FILM RELATED FORMULATION [6-18]

Country	Patent Number	Title	Inventor
US	5948430	Water soluble film for oral administration with instant wettability	Zerbe et al.
US	6159498	Bioerodable film for delivery of pharmaceutical compounds of mucosal surfaces	Tapolsky et al.
US	6596298B2	Fast dissolving orally consumable film	Leung et al.
US	6824829B2	Process for manufacturing thin film strip	Berry et al.
US	7132113B2	Flavored film	Zerbe et sl.
US	7182964B2	Dissolving thin fim xanthone suppliment	Kupper et al.
US	7241411B2	Thin film strip	Berry et al.
US	7267718B2	Pullulan film composition	Scott et al.
US	7347985B2	Breath freshening and oral cleansing product with magnolia bark extract	Maxwell et al.
US	7579019B2	Pharmaceutical carrier device suitable for delivery of pharmaceutical compounds to mucosal surface	Tapolsky et al.
US	1648712B2	Fast dissolving orally consumable film containing taste masking agent	Bess et al.
US	7946296B2	Dissolvable tobacco film strip and method of making the same	Wren et al.
US	4136145	Medicament carriers in the form of film having active substance incorporated there in	Fuchs et al.

COMPOSITION OF MOUTH DISSOLVING FILM[19]

A typical composition of mouth dissolving film contain following polymer.

Composition	Concentration
Drug	1-25%
Water soluble polymer (film forming agent)	40-50%
Plasticizers	0-20%
Fillers, colours, flavours	0-40%

Active pharmaceutical ingredients

The API used in formulation of the film is in the percentage of the 1-25% with small dose. The micronized API is best suitable candidate for the formulation of the thin film which improves dissolution rate and uniformity in the film[20]. For poorly water insoluble drugs the film is prepared by increasing solubility by complexation with various cyclodextrin. The poloxamer 407 is surfactant used to increase solubility with this complexes[21.] Following are some drug candidate which are used in mouth dissolving film formulation[22-26].

Drug Molecule	Category
Rofecoxib	NSAID
Cetrizine hydrochloride	Anti-histaminic
Etophyline	Bronchodilator
Montelukast sodium	Asthma/Allergic rhinitis
Meclizine Hydrochloride	Anti-histaminic
Fentanyl	Analgesic
Metoclopramide	Anti-emetic
Ambroxol hydrochloride	Mucolytic Agent

Film forming Agents:

Film forming agents are water soluble polymers which are used in formulation of thin film. These are HPMC E5, HPMC E15, HPMC E50, Microcrystalline Cellulose, gelatin Polyvinyl alcohol, Gelatin, Eudragit, Maltodextrin, Pullulans [27].

Plasticizers

The plasticizers are used in the formulation of mouth dissolving film to increase the flexibility by reducing the glass transition temperature of the film. Improper use of plasticizers may affect the mechanical properties of the film. The commonly used plasticizers are PEG 400, Glycerol, Propylene Glycol, Acetyl citrate castor oil etc [28].

Sweetening agents

The sweetening agent used in formulation of mouth dissolving film is used for the purpose of taste masking of some bitter drug and good mouth feel. The commonly used sweetening agents are Fructose, Sucrose, Maltose, Neotame, Aspartame, Mannitol, Sorbitol, Glucose [29]. Neotame and Aspartame is sweeter than sucrose. Acesulfame-K and sucralose have more than 2000 and 8000 times sweetening power as compared to sucrose. Rebiana which is an herbal sweetener, derived from plant stevia rebaudiana(south African plant) has more than 200-300 time sweetness but these synthetic sweeteners carry a disadvantage of after taste effect which can be reduced by mixing or blending the natural and synthetic sweeteners. The amalgation of sweeteners may lead to synergism and improvement in of the formulation [30].

Saliva stimulating agents[31-32]

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the strip.

Surfactant

Surfactants are used as solublising or wetting or dispersing agent so that the film is getting dissolved within seconds and release active agent immediately. Some of the commonly used are sodium lauryl sulfate, benzalkonium chloride, bezthonium chloride, tweens etc. One of the most important surfactant is polaxamer 407 that is used as solubilizing, wetting and dispersing agent[33].

Colouring agents

Pigments such as Titanium dioxide or FD & C approved colouring agent are incorporated (not exceeding concentration of 1% w/w) in solution.

ORAL FILM MANUFACTURING METHODS[34]

The oral film manufacturing process includes

1. Solvent Casting Method
2. Hot –Melt Extrusion
3. Solid Dispersion Extrusion
4. Rolling Method

1. Solvent Casting Method

The steps in involved solvent casting method are

- Water-soluble hydrocolloids (polymer) are dissolved to form a homogenous viscous solution
- API and other ingredients are dissolved in smaller amounts of aqueous solvent using a high-shear processor
- The entrapped air is removed from the viscous solution by vacuum
- Coated on a non-treated casting film
- Sent to aeration-drying oven and subsequently wound onto roll stock.
- As described in Figure2

2. Hot Melt Extrusion

- The API and other ingredients are mixed in a dry state
- Filled in the hopper
- Conveyed, mixed, and melted by the extruder
- After being subjected to the heating process and extruded out in a molten state, a die then shapes the melt in the required film form.
- As described in Figure 3.

3. Rolling method

In rolling method solution or suspension containing drug is rolled on carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on rollers (Fig:4)and cut into desired shape and sizes [35.]

EVALUATION TEST FOR MOUTH DISSOLVING FILM[36-38]

1. Uniformity of dosage units of the preparation

The uniformity of dosage units of the oral film preparation was tested using 20 preparations, and the content of drug was determined by analytical method. The acceptance value (AV) of the preparation is less than 15%, according to the JP15 (Japanese pharmacopoeia) . AV for JP15 was calculated according to the following Eq.

$$AV=[M-X]+ks$$

where M is label claim (100%), X is the average (%) of individual contents, k is the acceptability constant (2.2), s is the standard deviation. In USP27, the contents of major component in the preparation should be within a range between 85% and 115% and the relative standard deviation should be less than or equal to 6.0%.

2. Thickness

The thickness of strip can be measured by micrometer screw gauge at different strategic locations. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip.

3. Tack tests

Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. The alternative name for this test is dryness test. With help of this test film is checked for dry to handle, dry to touch, dry to print, dry to recoat.

4. **Tensile strength**

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

Tensile Strength = Load at Failure X 100 / Strip Thickness X width

5. Percent Elongation

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

%Elongation = Increase in length of strip x 100 / Initial length of strip

6. Tear resistance

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51mm (2 in.)/min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required to tear the specimen is recorded as the tear resistance value in Newton's (or pounds-force).

7. Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young modulus = Slope x 100 / strip thickness x cross-head speed

ard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

8. Folding Endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

9. Disintegration Time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films/strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s.

10. Dissolution Test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

11. Assay/drug content and 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%.

Figure: 1 Evolution of Film

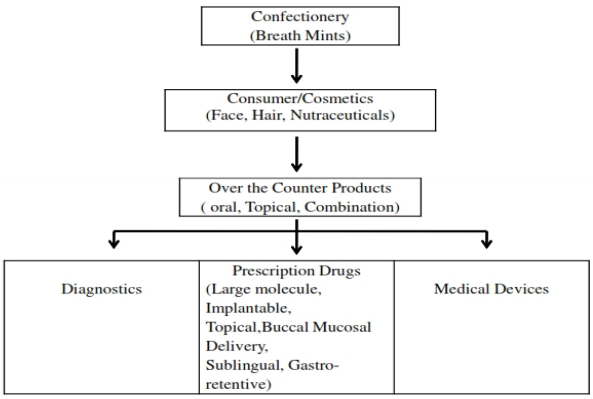


Figure: 2 Solvent Casting Film Systems

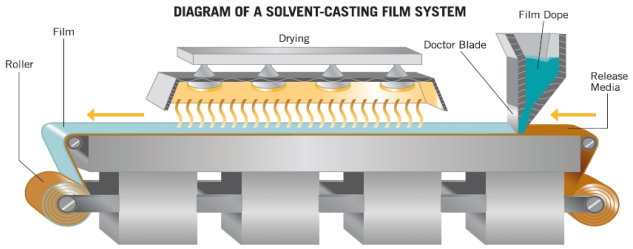


Image Source: Particle Science

Figure: 3 Film Extrusion System

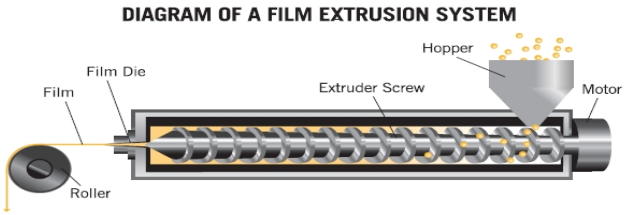
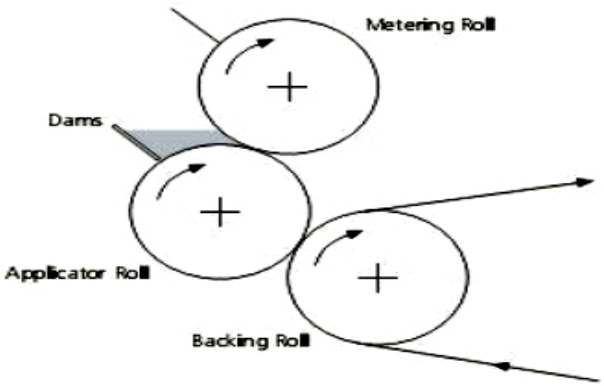


Image Source: Particle Science

Figure: 4 Rolling Method



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