Saket Pathak et al /J. Pharm. Sci. & Res. Vol. 12(8), 2020, 1131-1139

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Recent Updates on Orally Disintegrating Thin Films

Saket Pathak, Gaurav Goyal, Vineet Kumar Rai, G. D. Gupta*
ISF College of Pharmacy (An Autonomous College), Moga India

Abstract

Oral thin film have recently acquired major impact due to its properties such as rapid dissolution rate, newly launched formulation orally fast dissolving films (OFDFs). This is convenient and easy to use compared to other delivery types such as orally disintegrating tablets. This technology has established clothing and oral healthcare products in the form of breath strips over the past few years and has become a new and generally recognized source of consumer interest in OFDFs for a significant number of pharmaceutical industries. It is a kind of delivery method made using hydrophilic polymers. When thin film is keep on Tongue disintegrate and dissolve in very less time without intake of water. And the loaded API is release in few seconds. Oral film made from polymer, humectants, plasticizers, sweetener, sweetening agents, opacifier, flavoring agent and solvent. The formulation are evaluated on the flowing bases Thickness, Dryness/tack test, Tensile strength, Folding endurance, Organoleptic test, Swelling test, Surface pH test, Assay/Content Uniformity, Disintegration test, In-vitro Dissolution test. This review will give overview of the different formulations, rapidly dissolving oral thin film preparation and quality assurance processes.

Key words: Oral; thin film, disintegration, drug delivery

INTRODUCTION

Fast Dissolving Thin Films is gaining fascinating interest and adoption in the pharmaceutical industry nowadays due to greater flexibility and comfort. The idea of films dissolving the mouth arose from the transdermal patch platform. Fast Dissolving Thin Films can be used as an alternative to a rapidly dissolving tablet by showing the behavior of either dissolving or disintegrating in salivary fluids without the need for water when put on the tongue Intra-oral absorption enables the rapid start of the operation [1]. The issue with swallowing tablets was much more problematic for pediatric and geriatric patients, and also for traveling patients who would not have available access to water. And, in the late 1970s, rapidly dissolving drug delivery systems came into being [2].

The development of Fast Dissolving Thin Films as an alternative to capsules, tablets and syrups. Such systems contain of solid dosage materials, which easily disintegrate and dissolve in the oral cavity without water administration.Rapid-dissolving oral thin film is a solid dosage medium that disintegrates or dissolves in a few seconds when put in the mouth or tung without water drinking or chewing.After disintegrating in the oral cavity, the therapeutic effect of the drug has been improved by pre-gastric absorption from the pharynx and esophagus of the mouth as the saliva goes down into the gut [3]. In such cases, the drug's bioavailability is significantly higher than that seen from standard tablet dosageThe oral route is the preferred route for the distribution of the drugs than many other routes. But oral drug delivery systems will need some improvements due to their certain limitations related to specific patients that include pediatric, geriatric and dysphasia conditions along with many health conditions because they have trouble swallowing or chewing solid dosage forms.Most geriatric and pediatric patients are having trouble taking solid preparations because of the risk of choking. Even with quick dissolving tablets due to their presence there is a risk of choking. One study found that nearly 26 percent of 1576 patients had difficulty swallowing tablets. The first and most frequent complaint was the size, texture and taste of tablets [4].

There are a number of polymers required for the ODF preparation. The polymers may be used to achieve the required film properties on their own or in combination. The films produced should be sufficiently tough to prevent damage during transportation or during handling [5]. The inert ingredients used in ODF are usually water-soluble in nature while the drug could be either water soluble or lipid soluble in nature. Because the most basic and significant part of the ODFs is the film-forming polymer (which forms the basis for the ODFs), And plasticizer is the most important and essential ingredient of ODFs. A minimum of 40-50 percent w / w of polymer and up to 20 percent of plasticizer (overall weight, polymer) will typically be present based on the overall weight of dried ODFs [6]. The different synonyms employed for FDFs consist of), orally disintegrating films (ODFs), mouth dissolving films (MDFs), melt in-mouth films, quick dissolving and rapid disintegrating films, oral-dispersible films, melt in-mouth films [7].

Advantages

The oral thin films dissolves easily in contrast with other traditional dosage forms. These are less in weight and easy to handle compared to orally quickly disintegrating tablets that require special packaging. Similarly, an individual dose of the strip can be packed separately without any of the secondary container being needed. No need of shaking before administration like aqua's dosage form. it may contribute more acceptance by the patients. Oral thin film is extremely useful for elderly, pediatric and psychiatric patients as it is simple to administer and minimize the risk of suffocation and thus guarantees patient safety. In addition, oral thin films also can be beneficial for bedridden and un-cooperative patients, because they can be easily administered and hardly spit out. The oral thin films are useful when fast action is needed, for example Coughing, asthma or bronchial, motion sickness, allergic attack, Hypertension [8,9,10].

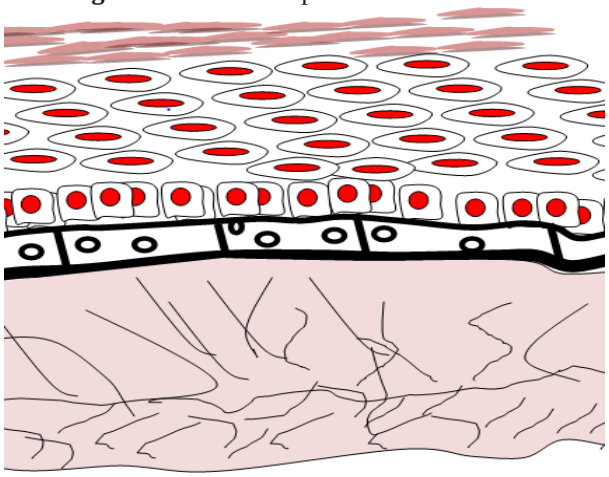
Limitations

The main limitation of the oral thin film is only administrated those drugs who are pharmacological effective at less dose. They are hygroscopic in nature so it can easily absorb the moisture. It means special packaging is required for long time preservation. A combination of more than one drug is very challenging in the oral thin film because they effect the dissolving and disintegration time of filming. Difficulty to distribute a uniform dose in every film. Thermolebile drug are not easily load in the film because they can not dry in hot oven or hot plate so they required alternative method of drying [11,12].

The oral mucosa consist three layers of cells

Oral Epithelium is known by Stratified squamous epithelium. It is the outer layer of the oral mucosa. It consists of epithelial cells. it is arranged on the basal membrance (Figure 1). the inner most layer are contact with the basal membrane. other layer is arrenge one another to maintain structure. Lamina Propria consists of loose connective tissue. It is Present below the stratified epithelium layer. Sub Mucous Membrane is the internal layer of oral mucosa.it is the layers of irregular or loose connective tissue. It joint the mucosa to underlying smooth muscle that support the mucosa and give the strength to mucosa [13,14,15].

Figure 1: Pictorial depiction of oral mucosa



Ingredients

The films contain up to 25% w/w of the drug. Various API can be dilliver by the oral thin film inculuding antiulcer, anti histamine, antitussive, expectorants, antihistamine and NSAIDs (Table 1). Small dose molecule are the best canidate in oral thin film [16,17]. The API loads into thin film have posses flowing properties.

1. Sow effect on low dose max dose up to 40 mg
2. Have no bitter test
3. Good stability in sliva
4. partially unionised at the sliva pH
5. Permeate the oral mucosa

Surfactant

Surfactant are use as wetting, dispersing and solubilizing agent so the films are dissolving within few seconds and immediately release the active ingredient. These are the generally use surfactant tween, , bezthonium chloride, benzalkonium chloride, sodium lauryl sulfate etc. polaxamer407 is the widely use polymer in thin film [18,19].

Polymers

For ODF preparation, a number of polymers are available. List of Polymers of natural and synthetic origin is given in table 2 and figure 2. AS the strip forming polymer (which forms the foundation for the FDF) is the most important and main ingredient of the ODF, at least 45% w / w of polymer should usually be required based on the overall amount of dry film, but usually 60 to 65% w / w of polymer must be preferred to achieve the required properties The polymers may be used alone or with a combination to achieve the required film properties. The film produced should be sufficiently tough to prevent damage when handling or shipping. The thickness of the films depends on the type of polymer and the quantity in the formulation. Fast dissolving film is formulated by using hydrophilic polymers that dissolve quickly on the oral or buccal cavity, transmitting the drug through dissolution to the systemic circulation when contact with liquid is made. For fast dissolving films, water-soluble polymers are used as film formers. The water-soluble polymers fulfill the films ' rapid disintegration, good mouth sensation and mechanical properties [20,21].

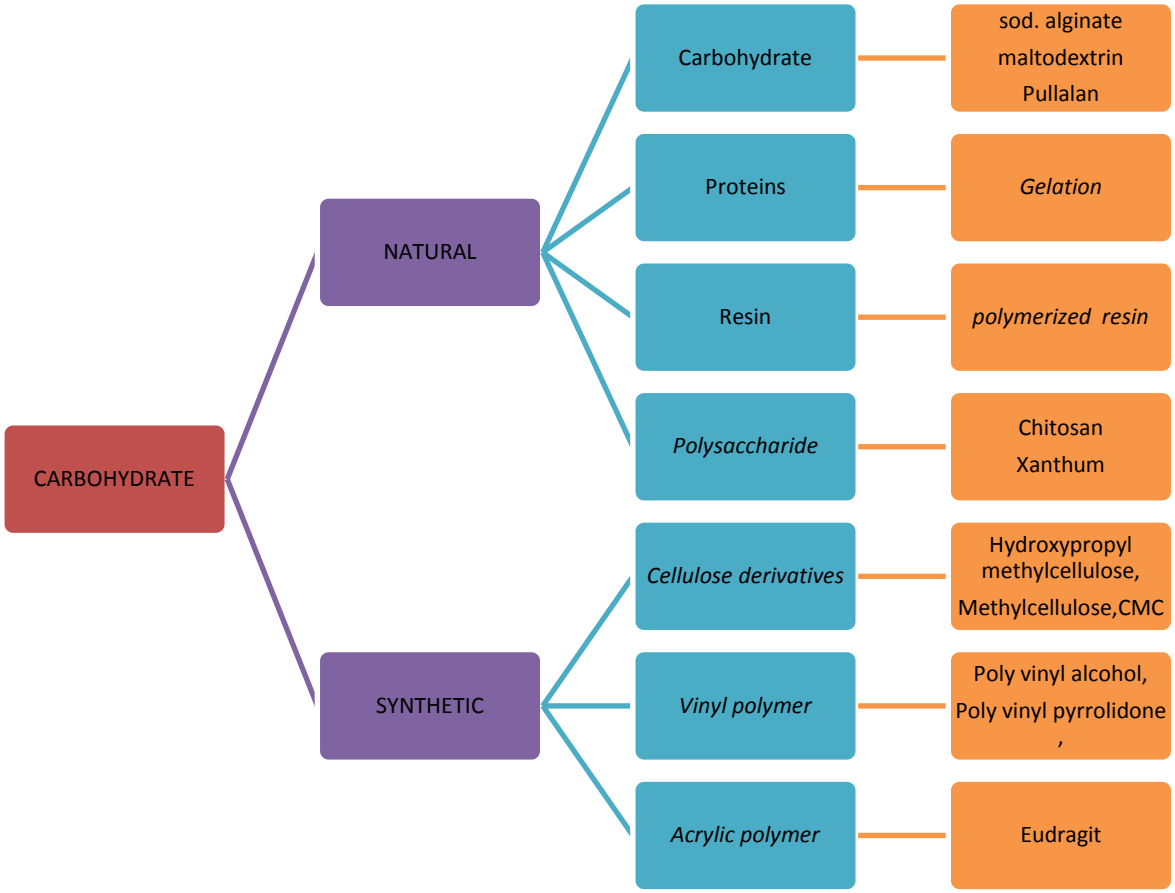
Table 1: ingredients used for oral thin film with required concentration

Ingredients	**Amount %(w/w)**
Drug	1-30%
Film forming polymers	40-50%
Plasticizers	0-20%
Saliva stimulating agents	2-6%
Sweetening agents	3-6%
Flavoring agents Qs	Qs
Surfactants Qs	Qs
Colors, filler Qs	Qs

Table 2: List of Polymers of natural and synthetic origin

Natural				***Synthetic***		
Carbohydrate	*Proteins*	*Resin*	*Polysaccharide*	*Cellulose derivatives*	*Vinyl polymer*	*Acrylic polymer*
sodium alginate	Gelatin	Polymerized rosin	Chitosan Xanthan	Hydroxypropyl methylcellulose (E3, E5, E15, K3, K15, K50),	Poly vinyl alcohol,	Eudragit (RD-100, 9, 10, 11, 12 and RL-100)
maltodextrin,				Carboxy methylcellulose	Poly vinyl pyrrolidone (K-90, K-30)	
Pullalan,			Xanthan	Methylcellulose (A3, A6, A15),	poly ethylene oxide	
pectin,				Sodium carboxymethyl cellulose		
Sodium starch glycolate				Microcrystalline cellulose		

Figure 1: Pictorial depiction of polymers used of natural and synthetic origin



Plasticizer

Plasticizer are use in the film for enhance the mechanical properties. It improves the elongation and tensile strength by change the glass transition temperature of polymer. It reduces brittleness and improves flexibility. in proper use may cause blooming and cracking. The Quantity of polymer use 0 to 20 % of dry weight of polymer choice of plasticizer depends on types of polymer, solvent use in the formulation. It also depends upon compatibility with polymer. Some of the polymer generally use in the formulation are Glycerol, Propylene glycol, Low molecular weight polyethylene glycol, sorbitol, castor oil, acetyl triethyl citrate (ATEC), , triethyl citrate (TEC) [22,23,24,25].

Sweeteners

Sweeteners are use to mask the bitter taste of drugs. They are use in the concentration 3 to 6 % w/w. they are use alone or in the combination of two or three. sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose

are the classical source of polymer. Polyhydric alcohols such as isomalt sorbitol and , mannitol can be utilized as a part of mix as we feel cooling sensation. galactose mannose, glucose, , fructose, xylose, ribose, , maltose dextrose, sucrose, sugar, xylitol, sorbitol mannitol and soluble saccharin salts, cyclamate saccharin, acesulfam-K, Aspartame, Neotame respectively [26,27].

Flavors

The flavors improve the formulation's acceptance and boost the film's elegance property .The OFDF formulations ideally add up to 10 percent w / w flavors. The acceptance by a person of the oral disintegrating or dissolving formulation depends largely on the initial quality of the flavor that is detected in the first few seconds after ingestion of the drug and the after taste of the formulation that lasts for at least 10 minutes. Flavor selection depends on the type of drug to be included in the formulation. Aging has been found to play an important role in the fondness of the taste. Geriatric groups such as lemon or strawberry flavours, whereas younger generations such as fruit punch, raspberry, etc. It is possible to select flavoring agents from synthetic flavor oils, oleo resins, extracts from different parts It is possible to select flavoring agents from synthetic flavor oils, oleo resins, extracts from various parts of plants such as leaves, fruits and flowers.Types of flavor oils include peppermint oil, cinnamon oil, nutmeg oil, while tea, cocoa, coffee, chocolate and citrus flavours. Apple, raspberry, cherry and pineapple are just a few examples of the type of fruit.[28,29]

Saliva stimulating agents

The aim of using saliva stimulating agents is to boost the rate of saliva secretion which would allow the rapidly dissolving film to disintegrate more quickly. These agents can be used in conjunction or alone. These are used in the concentration of 2 to 6 percent w/w of the film generally, acids used in food preparation can be used as salivary stimulants.lactic acid, Citric acid ascorbic acid, malice acid tartaric acid, are generally used to stimulate saliva. citric acid being the most preferred amongst them [30,31].

Cooling agents

cooling agents such as monomethyl succinate add to increase the flavor strength and enhance the product's mouth-feel effect. we can also use other cooling agents such as WS23WS3, and Utracoll II in combination with flavors [32,33].

Colors

A entire range of colors is available FD&C colors, EU colors, natural coloring agents and natural juice concentrate, pigments such as titanium oxide, silicon dioxide and zinc dioxide, and custom pantone compatible colors. Such coloring agents should not reach 1 percent w / w concentration levels. Some agents are used in the presence of insoluble or suspensive ingredients or drugs.

Evaluations

Thickness

The thickness of film is directly proportional to dose uniformity of film. Uniformity of film may vary in the loaded amount of mint in films. Check the thickness of film by Digital Screw Gauge or calibrated digital Vernier Calipers. at five different location an the mean value is calculated which is the final thickness of the film. It should be in the range of 0.045 mm to 0.065 mm [36,37].

$$\text{Thickness} = \frac{T1 + T2 + T3 + T4 + T5}{5}$$

Average weight

About 20 film are weighed individually. The average weight was determine by the add the weight of all film and divided by 20 [38,39].

$$\text{Average weight} = \frac{\text{weight of 20 strips}}{20}$$

Uniformity of weight

After calculating the average weight calculate individually the % weight of film agents the average weight. The individual weight should not deviate more than ± 10% significantly from the average weight [40].

$$\text{uniformity of weight} = \frac{\text{weight of individual strip}}{\text{Average weight of strip}} * 100$$

Disintegration time

Disintegration test was performed in the USP disintegration apparatus. One film placed in each tube and the basket rack is positioned in 1 L beaker of water at 37 °C ± 2 °C. note the Disintegration time all the film should disintegrate in 30 second move the basket up and down at the a frequency of 30 ± 2 cycles per minute. The average disintegration time of six films from each formulation was noted [41,42].

pH of film

A combined pH electrode was used for this purpose. Oral strip was slightly weight and dissolve in the water. Weight 1 gram of film and dissolve in 100 ml of water. The pH was measured by bringing the electrode in contact with the solution of the oral film. The experiments were performed in triplicate, and average values were reported It should be 7 to 9.[43,44]

Folding endurance

The folding endurance was measured manually for the prepared films. Cut the film and fill in the pouch.Roll the pouch 5 times and press after opening the roll pouch, the strip should be intact [45,46].

Water content

The water content determine by the by KBR. This technique is based on the quantitative reaction between iodine and sulfur dioxide by addition of water in presence of methanol It should not more than 10 % W/W [47,48].

Organoleptic evaluation

Organoleptic evaluation Since the ODFs are intended to disintegrate rapidly in oral cavity, the product needs to have accepted organoleptic palatable characteristics. Organoleptic evaluation of prepared ODFs are carried out on panel of healthy volunteers with sound organoleptic senses, with their prior consents. The ODFs is rated on the basis of taste, mouth feel (grittiness or smoothness) and physical appearance [49].

Moisture loss

Percent moisture loss is a parameter that determines the hygroscopicity of a film. Usually, this parameter is determined by first finding the initial weight of the film, afterwards, putting this film in a dessicator for three days.

After three days, strips are taken out and weighed again. Moisture loss is determined by applying the following formula[50,51]

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

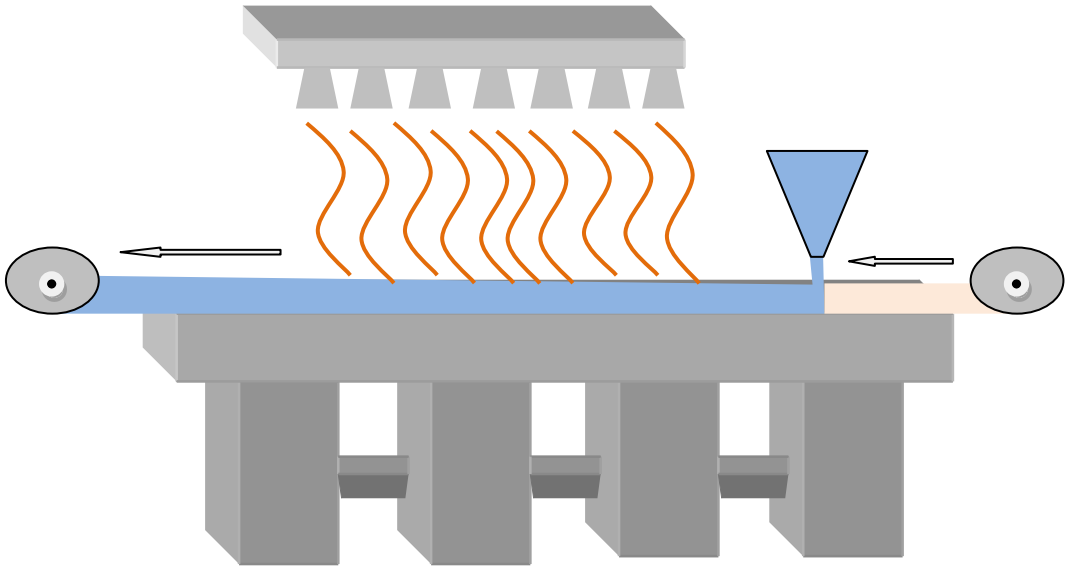
Moisture uptake

Moisture uptake of a film is determined by first cutting the film with the dimension of 2 x 2 cm^2. Afterwards these strips are exposed to environment with a relative humidity of 75% at room temperature for 7 days. Moisture uptake is determined as percent weight gain of the strips[51]

$$\text{Percentage moisture uptake} = \frac{\text{Final weight} - \text{Initialweight}}{\text{Initial weight}} * 100$$

Marketed Product [52,53]

Manufacturer/ Distributor	**Brand name**	**API (strength)**	**Uses**
Solvay Pharmaceuticals	Klonopin wafers	Clonazepam (0.125mg, 0.25mg, 0.5mg, 1mg and 2mg.)	Treatment of Anxiety
Pfizer,Inc	Listerine Cool Mint Pocket Paks	Cool mint	Mouth Fresheners
WoltersKuwerHealthInc	Sudafed	Phenylepinephrine	Relieving Congestion
Innozen, Inc	Suppress	Menthol (2.5mg)	Cough Suppressants
Novartis	Triaminic	Diphenhydramine HCL(12.5	Anti-allergic
Novartis	Theraflu	Dextromethorphan HBR (15mg)	Cough Suppressant
Del	Orajel	Menthol/pec Mouth	Mouth
Novartis	Gas-X	Simethicone (62.5mg)	Anti Flatuating
Prestige	Chloraseptic	Benzocaine/ menthol(3mg/3mg)	Sore throat
Pfizer	Benadryl	Diphenhydramine HCL(12.5mg or 25 mg)	Anti-allergic



Methods of Preparation

1. Solvent casting method

Compare to other method he solvent casting method is easy cost effective feasible and widely use. In to the solvent casting method water soluble biodegrable polymer are dissolve in the water or organics solvent with the help of continuous string. After the complete dissolve the polymer and finally add the API with continuous mixing. Apply vacuum for remove the air bubble form solution. Cast the film and dry at higher to lower temperature. This are the quality control parameters in The manufacturing procedure of thin films temperature and viscosity of polymer solution, Air entrapment in solution, drying temperature, moisture control and thickness.[54,55]

2.Hot melt extruder

Hot melt extruder is used in this process. This technique involves shaping a polymer into a film via the heating process. A blend of pharmaceutical ingredients including API in dry state is filled in the hopper, conveyed, mixed and subjected to the heating process, and then extruded out in molten state melted by the extruder. The molten mass thus formed is used to cast the film. It is completely anhydrous process use when water or organic solvent is not required. Very less no of literature are reported about

this method .It is the substitute method of solvent casting method. but this is not suitable for thermo labile drug because in this method all the exceptions are firstly melt on high temperature then cast the film. in HME avoid the need of organic solvent so it is environment friendly. In HME polymer, drug substance and other excipetents are filled in the hopper mix all properly an apply heat then extruded out the molted state by extruder. Cast the film and cut in proper size and shape.[56,57] It is cost effective, require less time for the production and less number of unit operation.

3.Semisolid Method

This method are prefer when acid insoluble polymer are use in the preparation of thin films. Acid insoluble polymers are cellulose acetate butyrate, cellulose acetate phthalate, The ratio of film former polymer and acid insoluble polymer should be used in the 4:1. In semisolid method the water soluble film former polymer is mix in the water. in second step the resulting solution is added in insoluble acid polymer like acetate phthalate, cellulose acetate butyrate. Then the required amount of plasticizer are added for obtained the gel mass. Then sonicate the solution for removal the air bubble. Finally cast the gel mass in to the ribbon or films By the heat controlled drums. The thickness of film should be 0.015 to 0.05 inches finally cut the film in required shape and size [58,59]

4. Solid Dispersion

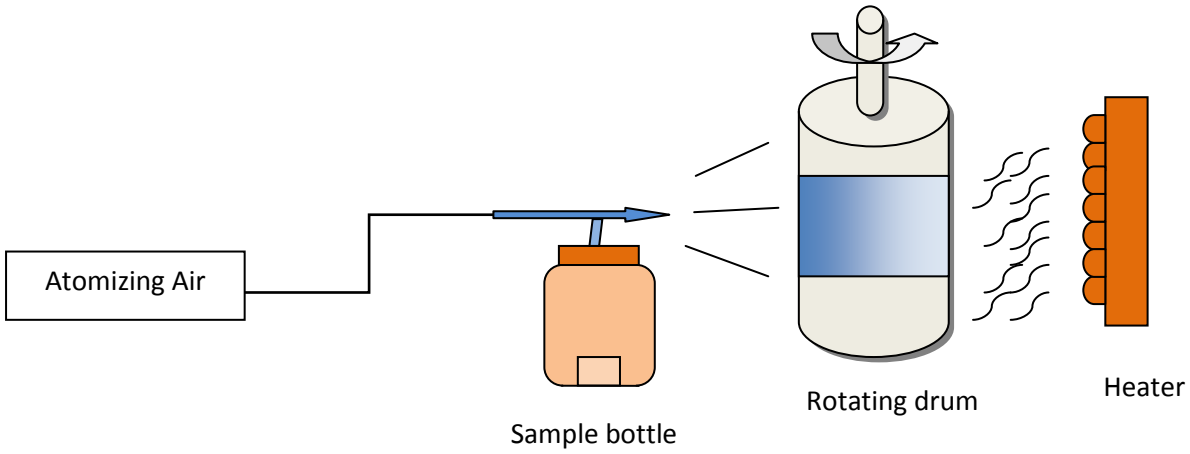
Solid dispersion refers as the dispersion of two or more than two in an inert carrier in to amorphous hydrophilic polymers. The API are dissolved in a suitable solvent. Then the API solvent is incorporated into the melt of polyethylene glycol suitable polymer. Without removing liquid solvent blew 70 ◦ C. then finally solid dispersion are shaped into films by a means of dies [60,61].

5. Rolling Method

In to the rolling method water is manly used as solvent. Some time it also use with the combination of organic solvent. The polymer solution containing drugs are rolling on the roller. The film are dried on desired temperature and finally cut and packed [62,63,64].

6. Spray Technique

API, polymers, as well as all other excipients are dissolved to form a clear solution in a suitable solvent. This resulting solution is then sprayed onto appropriate materials like glass, non-siliconized Kraft paper polyethylene film or Teflon sheet



Packaging of Thin Film

In pharmaceutical industries the selection of packaging have important role for the preserve the intrigrity of drugs and exceptions. In to the case of thin film special care are required during storage, in-process and manufacturing. Because the film are made by the hydro flick polymers so easily absorbed the moisture. The film should be packed in to the air tight container or pouch so they do not absorbed the moisture and the films are not degrade. In to the last dissent aluminum foil are commonly used as packaging material. But now days various types of material use for packaging of thin film like plastic pouch, blister card, foils and papers.

1) Plastic Pouch

The flexible pouches are commonly used for single strip but sometimes it is use for two or three strips are packed in one pouch. The plastic pouch have lots of benefit like low packaging cost, easy filling, easy to handle, light weight. But plastic pouch is not environment friendly. It pollutes the environment.

2) Plastic box

Plastic box are used for packaging of multiple films in one packet. Ten to fifteen films should packed in to one box. It reduce the packaging cost and environment friendly. But thy should not stick to each other.

3) Blister

It consists of two components. First one is blister who have cavity for holding the strips and second one is lid stock that shield the blister. The lid stock is made from plastic and cavity are made form plastic [66,67,68,69,70].

Some of the patents on oral thin films are described in the Table 3

Table 3

S. No.	Patent No.	Year	Title
1	Us 10130684 B2	2018	Oral dissolving films for insulin Administration, for treating Diabetes
2	US 9980798 B2	2018	Packaged oral care implement
3	Us 9597287 B2	2017	Edible oral strip or wafer dosage Form containing on exchange Resin for taste masking
4	Us9603797 B2	2017	Oral and/or buccal composition in The form of a thin film of a cpc Weakly soluble active ingredient, Method of preparing same and use Of same
5	Us 9687445 B2	2017	Oral film containing opiate Enterc-release beads
6	Us 9539334 B2	2017	Orally Dissolving Thin Film Containing Allergens and Methods Of Making And Use
7	Us 9675548 B2	2017	Orally dissolving films
8	US 2016/0317462 A1	2017	Pharmaceutical microemulsion Mmobilized in a thin polymer Matrix and methods of making Themi
9	US 2016/0030335 A1	2017	Methods for modulating Dissolution, bioavailability, Bioequivalence and drug delivery Profile of thin film drug delivery Systems, controlled-release thin Film dosage formats, and methods For their manufacture and use
11	US 9167835 B2	2015	Dissolvable films impregnated with Encapsulated tobacco, tea, coffee, Botanicals, and flavors for oral Products
12	US 9095577 B2	2015	Stabilized amine-containing actives Noral filmi compositions
13	US 8999372 B2	2015	Methods for modulating Dissolution, bioavailability Bioequivalence and drug delivery Profile of thin film drug delivery Systems, controlled-release thin Film dosage formats, and methods for their manufacture and use.

CONCLUSION

Fast Dissolving Film has gained popularity in recent years as a dosage form, and is the most acceptable and accurate form of oral dosage that bypasses the hepatic system and shows more therapeutic response. Because of both customer compliance (especially pediatric and geriatric) and industrial acceptability. They combine the greater stability of a solid dose form with the good liquid applicability. Due to lower cost and consumer preference, oral films can replace the over-the-counter drug, generic and brand name from market. This technology is a great tool for controlling the life cycle of the product, to. the patent life of existing products.

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