CURRENT OVERVIEW OF ORAL THIN FILMS DRUG DELIVERY SYSTEMS

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ABSTRACT

Novel drug delivery systems have drawn more attention in recent years due to their potential to boost patient compliance, security, and safety and efficiency while also lengthening the life of a product patent life cycle. Several pharmaceutical companies have recently concentrated their research efforts on fast acting technologies. Most cutting edge oral solid dose form is quick dissolving oral thin films, which offers greater comfort and flexibility. It increases the effectiveness of active pharmaceutical ingredient by dissolving in the oral cavity in a matter of seconds after coming into contact utilizing fewer saliva than fast dispersing tablets, without chewing, and without the requirement for water for administration. For the formation of oral thin films, a variety of chemicals are used, such as polymers, active medicinal compounds, film stabilizing agents, plasticizers, surfactants, sweeteners, flavors, colors and salivary stimulate agents. Information in the current review relates to the formulation components, methods, and results of studies used to create fast dissolving oral thin films. Meanwhile, the market for fast dissolving oral thin films is well positioned for future expansion. The market for oral thin films appears to be poised for major growth.

Key words: Oral thin film, Novel drug delivery system, Oral mucosa, Polymers.

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1. INTRODUCTION

Oral administration is the most commonly employed method to provide therapeutic drugs among the many routes since it is simple to administer and results in high patient compliance. In total, solid dosage forms make up around 60% of the formulations. Tablets and capsules are the most often used oral solid dose forms. The traditional oral dosage form is typically problematic for elderly, young patients, and patients who are bedridden or travelling without ready access to water. The fear of choking prevents many pediatric and geriatric patients from taking solid medications. Due to its tablet-like form, there is a danger of choking even with rapid dissolving tablets. In order to solve this issue, a unique formulation known as oral quick dissolving films was created (Bhupinder Bhyan *et al*., 2011, Swapnil L. Patil *et al*., 2014, Nishi Thakur *et al*., 2013).

Because they consist of water-soluble polymers while they are placed in the cavity of the mouth or on the tongue, oral disintegrating/dissolving films or strips are described as drug delivery systems that are rapidly disintegrating the drug by dissolving or adhering in the mucosa with saliva within a few seconds (Hussain *et al.,* 2017, Mahboob *et al.,* 2016).

Oral thin film is described as including one or more active pharmaceutical substances, a flexible and non-brittle strip that can be placed on the tongue before passing into the gastrointestinal tract, aiming for a quick disintegration or dissolution in the saliva (Kathpalia *et al.,* 2013).

Rapidly disintegrating buccal films provide a convenient method for systemic drug delivery to solve this issue. Bypassing the first pass effect and having a well-supplied arterial and lymphatic drainage, greater permeability and higher systemic bioavailability are the effects. The oral mucosa is a very desirable and practical site for systemically drug delivery because to its enormous surface area of absorption, ease of consumption, and pain avoidance (Amir *et al.,* 1998, Satishbabu *et al.,* 2018). The mucosa of the buccal region is the transmucosal pathway that is best for both local and systemic medication delivery. (Akbari *etal.,* 2004, Remunan-Lopez *et al* .,1998).

Based on the transdermal patch technology, mouth-dissolving films are a revolutionary drug delivery device for oral drug administration. A extremely thin oral strip serving as the delivery mechanism can simply be placed on the patient's tongue or any other oral mucous membrane. Upon being instantaneously moistened by saliva, the film quickly hydrates and binds to the application site. The drug is subsequently released and quickly dissolves and disintegrates for oral mucosal absorption (Vollmer *et al.,* 2006).

For juvenile and elderly patients who struggle to swallow typical oral solid-dosage forms, fast-dissolving drug delivery systems were developed in the second half of the 1970s as a substitute to capsules, tablets, and syrups (Galey *et al.,* 1976). Zuplenz (ondansetron HCl, 4–8 mg), the first authorized oral thin film, was initially given in 2010. The next accepted medication Suboxon (buprenorphine and naloxan) was adopted immediately (Kathpalia *et al.,*2013).

The ideal fast dissolving oral thin film should have the following qualities (Aggarwal *et al.,* 2011)

- ❖ It ought to have a satisfying mouth feel
- ❖ It ought to work well with the other components
- ❖ A pleasant flavor

- ❖ It ought to be able to withstand environmental changes
- ❖ It should leave the least amount of residue in the mouth after oral delivery, if any
- ❖ It must immediately disintegrate in order to instantly release the medication in the mouth
- ❖ It should be less fragile and have strong mechanical properties to survive handling after manufacture
- ❖ Provides fast onset of action in illnesses needing urgent intervention, such as allergic episodes like asthma and intraoral infections. Leaves a pleasant aftertaste in the mouth
- ❖ Increases the quantity and pace of medication absorption
- ❖ Increases the bioavailability of less soluble in water medicines, particularly by rapidly dissolving while providing a high surface area
- ❖ Does not interfere with everyday activities like speaking and drinking
- ❖ Has a growing market and a wide range of products; offers administration of medications with a high risk of disruption in the gastrointestinal system.

Oral thin films have the following benefits (Sharma *et al.,* 2015, Kathpalia *et al.,* 2013, Karki *et al.,* 2016)

- ➢ It is simple to use
- ➢ Patients with mental illnesses and incompatibilities can easily apply
- ➢ Minimal dosage and adverse effects
- ➢ Safely employed even when access to water is not feasible (such as during travel)
- ➢ They are practical and don't utilize water
- ➢ There is no danger of suffocation
- ➢ Increased stability
- ➢ After utilization, there is little or no trace left in the mouth
- ➢ Avoids the gastrointestinal tract, enhancing bioavailability
- ➢ In comparison to liquid dose forms, it delivers a more precise dosing
- ➢ There's no necessity to measure, which is a significant drawback of liquid dose forms.

Disadvantages (Sharma *et al.,* 2015, Kathpalia *et al.,* 2013, Karki *et al.,*2016)

- ❖ Needs specialized packaging equipment
- ❖ Is unsuitable for drugs that wear out quickly and create irritation in the oral pH
- ❖ The quantity of medication that can be taken is minimal, although studies have shown that the weight-based API concentration could be raised by up to 50% (for instance, every single strip of Novartis Consumer Health's Gas-X® consists of 62.5 mg of simethicone)
- ❖ It's generally design hygroscopic. This makes it difficult to provide long-term protection
- ❖ However, drugs that are absorbed by a process of passive diffusion can be implemented in this manner
- ❖ Dose withdrawal is not possible while oral thin film is addressed quickly
- ❖ OTFs are not listed in any pharmacopoeia
- ❖ As compared to oral dissolving pills, preparation is more expensive.

1.1 ORAL THIN FILM CLASSIFICATION (Niyaz *et al.,* 2018, Mahboob *et al.,* 2016, Godbole *et al.,* 2018)

The oral thin film are classified into three ways and their characteristics distinguishing between oral thin films types from each other are represented in table 01.

a. Flash release (quick release)
b. Mucoadhesive melt away wafers (mucoadhesive wafer)
c. Mucoadhesive sustained-release wafers (mucoadhesive extended-release wafer).

Table 01: Characteristics distinguish various kinds of oral thin films apart from one another

CHARACTERISTICS	**FLASH RELEASE**	**MUCOADHESIVE MELT AWAY WAFERS**	**MUCOADHESIVE SUSTAINED REALESE WAFER**
Structure	Single layer	Single layer or Multilayer	Multilayer
Area(cm ^{2})	2-8	2-7	2-4
Application area	Lingual	Gingival or buccal region	Oral cavity or Others suitable areas in the gums
Thickness(mm)	20-70	50-500	50-250
Effect	Local or systemic effect	Local (or) systemic effect	Local (or) systemic effect
Excipients	Water soluble polymer	Water soluble polymer	Low solubility (or) insolubility polymer
Pharmaceutical phase	Solid dissolved (or) dispersed	Drug molecules in solid or suspended Form	Suspension, solid (or) dissolved /dispersed
Dissolution	60seconds	Gel consists in minutes	8-10 hours maximum

1.2 ORAL MUCOSA STRUCTURAL CHARACTERISTICS

The outermost layer of the mucous membrane of the oral cavity is made up of stratified squamous epithelium as shown in Figure 1. A basement membrane, a lamina propria, as well as the sub mucosa the deepest layer are located beneath this. By the way it starts with a mitotically active basal cell layer and progresses through a number of developing intermediate layers to the superficial layers, whereas cells shed from the epithelium's surface, the epithelium is comparable to the stratified squamous epithelia present throughout the rest of the body. (Shojaei *et al.*, 1998).

The oral mucosa as a whole obviously has a turnover time of 5–6 days, which has been assessed for the buccal epithelium. Based on the location, the thickness of the oral cavity mucosa differs: The mucosa of the buccal cavity ranges around 500–800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measures at roughly 100–200 µm. The epithelium make up changes according to the location in

the mouth cavity as well. The gingivae and hard palate mucosae are keratinized like the epidermis while contain neutral lipids known ceramides and acyl ceramides that have been linked to the barrier function. However, the mucosa of the soft palate, sublingual, and buccal areas are not keratinized (Harris *et al.,* 1998), which are comparatively water impervious and only contain trace levels of ceramide. A small quantity of neutral but polar lipids, primarily cholesterol sulphate and glucosyl ceramides, are also present in them. (Wertz et al.,1991, Squier et al., 1991, Squier et al.,1996). It has been discovered that non-keratinized epithelia are significantly more permeable to water than keratinized epithelia. The layer of oral mucosa is depicted from outermost to innermost in the figure1.

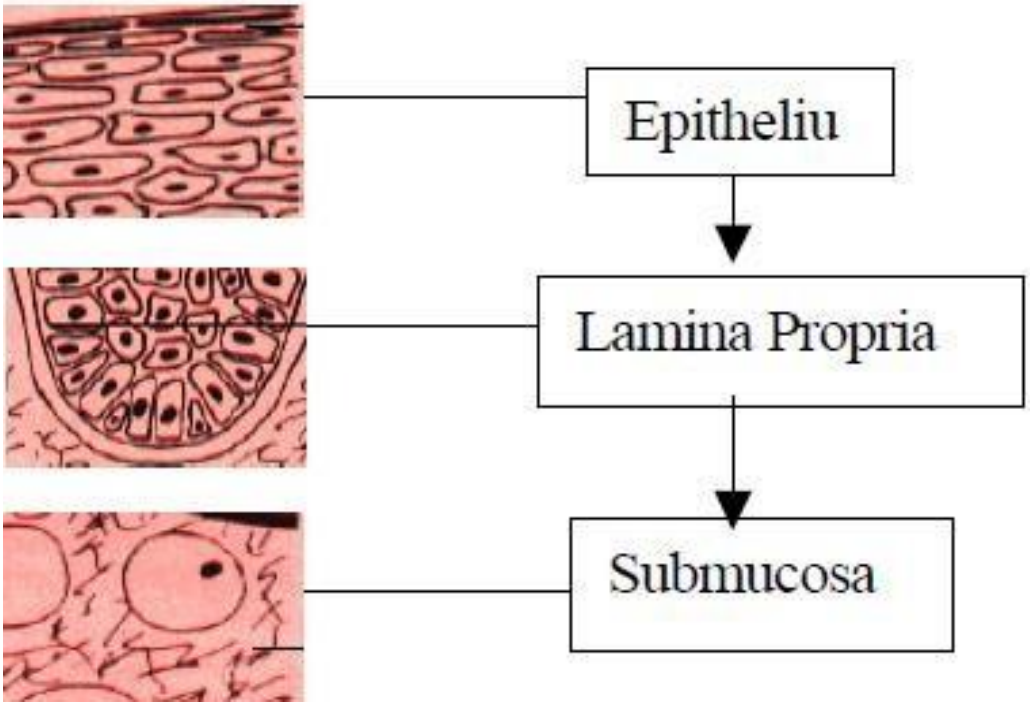

Figure 01: Layer of oral mucosa (Siddiqui *et al., 2011)*

PERMEABILITY

In regard to permeability, the oral mucosa lies in between the intestinal mucosa and the outermost layer of skin. According to estimates, the mucosa of the buccal cavity is 4 – 4000 times more permeable than the skin. (Galey *et al*., 1976). Because distinct oral mucosa have different shapes and functions, there are significant variances in permeability between different areas of the oral cavity (Harris *et al*., 1992). The permeability enhancer is crucial for the oral region's enhanced absorption of API. Therefore, a permeation enhancer is required as we are interested in absorbing the drug primarily through the mouth once it has been released from the formulation.

1.3 COMPOSITION OF ORAL MUCOSAL REGION

Oral mucosal cells

Carbohydrates and protein are the main components of the oral mucosa cell. It has an adhesive character and functions as a lubricant, reducing friction as cells move in relation to one another (Tabak *et al.*,1982). The bio adherence of mucoadhesive drug delivery devices is also

thought to depend on mucus (Peppas *et al.*,1985). While goblet cells produce and secrete mucus in other parts of the body, both the major and minor salivary glands secrete mucus as a portion of saliva in the oral mucosa. The small salivary glands can provide up to 70% of the overall mucin present in saliva (Tabak *et al.*,1982, Rathbone *et al.*,1994).

The presence of saliva, a digestive fluid that originates from three pairs of salivary glands (the parotid, submandibular, and sublingual glands), is an additional characteristic of the mouth cavity. Saliva contains 99% water and 1% organic and inorganic substances. Salivary amylase, a digestive enzyme, converts long chains of glucose molecules from starch into shorter chains. Many of the compounds found in plasma are present in saliva since it is generated from blood plasma. The primary predictor of salivary composition is flow rate, which in turn depends on three variables: the time of day, the kind of stimulus, and the intensity of the stimulus (Tabak *et al.*,1982, Rathbone *et al.*,1994).

The pH of the everyday saliva is between 5.5 and 7. The amount of liquid available to hydrate oral mucosal dosage forms is equal to the daily salivary volume, which ranges from 0.5 to 2 litres. The fact that the oral cavity is a water-rich environment is one of the key factors in the use of hydrophilic polymeric matrices as vehicles for oral transmucosal medication administration.

1.4 Mechanism of Action

The user's tongue or any other oral mucosal tissue can serve as the delivery channel. Due to the hydrophilic polymer and other excipients present, the film is immediately moistened by saliva and quickly hydrates and disintegrates to release the drug for oral mucosal absorption as shown in figure 02.

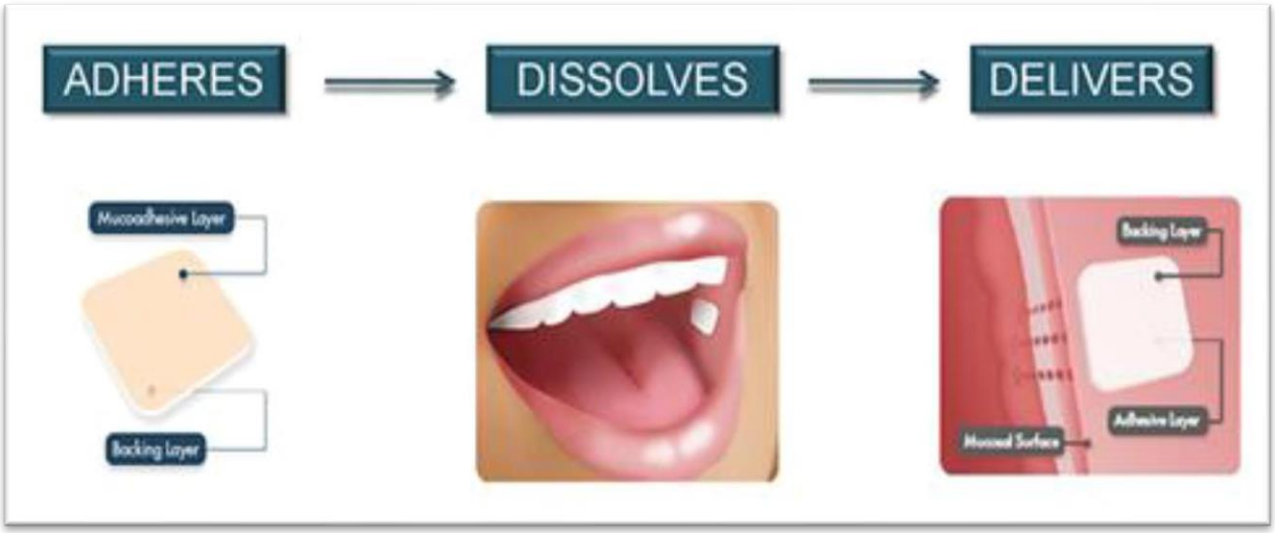

Figure 02: Mechanism of oral thin film (Rekha *et al ., 2014)*

1.5 FORMULATION AND THEIR COMPOSITION

An oral dissolving film is a thin, drug-containing film with a surface area of 5 to 20 cm^2. The maximum single dose of the medications that can be loaded is 30 mg. All excipients included in the formulation, from a regulatory standpoint, must be generally recognized as safe (i.e., GRAS listed) and authorized for use in oral pharmaceutical dosage forms. Plasticizer

considerations during formulation have been identified as significant determinants of the films mechanical properties. The composition of oral thin film and their quantities are listed in table 02. (Dnyaneshwar et al., 2014, Apoorva *et al.,* 2011). The following ingredients are typical of a formulation.

1. Drug
2. Film forming polymers
3. Plasticizers
4. Saliva stimulating agent
5. Sweetening agent
6. Flavoring agent
7. Surfactant
8. Colouring agent

Table 02: Composition of oral thin film (Khatoon *et al*., 2013)

S.NO.	**NAME OF THE EXCIPIENT**	**QUANTITY**
1	Drug	5-30%
2	Film forming polymer	40-50%
3	Plasticizer	0-20%
4	Saliva stimulating agent	2-6%
5	Sweetening agent	3-6%
6	Surfactant	Q.S.
7	Flavouring agent	Q.S.
8	Colouring agent	Q.S.

1.5.1 Active pharmaceutical ingredient (API)

The active pharmaceutical ingredient makes up between 30 and 40% of the film's unique composition. The ideal choices for fast dissolving buccal films include medications that are powerful, exhibit a high first-pass metabolism, and have non-compliant patients (Apoorva Mahajan *et al.,* 2011). API is usually beneficial because it will enhance the film's texture and also promote improved dissolving and uniformity in the oral fast dissolving films. Particularly for paediatric medicines, this renders the formulation unpleasant. Consequently, the taste must be covered up before the API is added to the Oral fast dissolving film. To make the formulation more palatable, a number of techniques can be applied. Most common procedure among the ones used entails combining and processing excipients withpalatable tastes with API that has a bitter taste. This is frequently referred to as an obscuration method (Mashru *et al.,* 2005, Gohel *et al.,* 2007, Koland *et al.,* 2010, Singh S Gangwar *et al.,* 2010, Jyoti, A *et al*., 2011, Kulkarni *et al* ., 2003, Juliano *et al* .,2008).

The choice of API is based on its potency, dosage, and therapeutic effectiveness. The most effective API for treating oral thin film include medications for erectile dysfunction, anti-alzheimer's, anti-parkinsonism, anti-tussive, antihistaminic, antiepileptic, expectorants, antianginal, antiemetic, neuroleptics, and cardiovascular agents (Ghodake *et al.,* 2013).

IDEAL CHARACTERISTICS OF DRUG TO BE SELECTED (Bhupinder Bhyan *et al.,*

2011)

- Drugs with a small to moderate molecular strength are preferred, with a maximum dose of 40 mg
- In addition to being partially unionized at the pH of the oral cavity, a drug should be stable and soluble in both water and saliva
- Must be capable of penetrating oral mucosal tissue.

1.5.2 Film forming polymers

The primary component of the oral rapid dissolving film is polymers. The quantity and type of polymer determine how robust the film will be. The acquired film needs to be durable enough to prevent damage during handling or shipping. In general, 45% of the dry film's total weight in polymer is utilised. The oral strip mainly utilizes hydrophilic polymers because, when in contact with saliva, they quickly breakdown in the mouth cavity. To achieve the desired film qualities, either one polymer or a mixture of polymers can be utilised. Pullulan is a polymer made from natural materials that can be obtained from sources other than animals and doesn't need to be chemically altered. In order to reduce the overall expenditure of the product, pullulan can be replaced with starch to the extent of 50 to 80 w/w during the production of fast-dissolving films. Maltodextrins and microcrystalline cellulose were combined as well to create fast-dissolving films. The outcome of the disintegration period of the film is greatly influenced by the physicochemical properties of the polymer / polymers chosen for the film formulation. Some of the film forming polymers are listed in the table 03 (Bhupinder Bhyan *et al.,* 2011, Kulkarni *et al.,* 2010, Arunachalam *et al.,* 2010).

Ideal characteristics of the film-forming polymers include: (Pathare *et al.,* 2013, Kalyan *et al.,* 2012)

- The polymer used should not be poisonous or irritating
- There should be no leachable contaminants in it
- It ought to have effective spreading and wetting qualities
- The polymer needs to have sufficient strength to peel, shear, and tensile properties
- The polymer should be easily accessible and reasonably priced
- It ought to have a long shelf life
- It shouldn't contribute to or worsen subsequent infections in the tooth or oral mucosa
- It ought to have a satisfying mouthfeel
- The ideal polymer would ideally possess local enzyme inhibitory effect in addition to penetration-enhancing properties
- It shouldn't present a barrier during the disintegration process.

TABLE 03: FILM FORMING POLYMER (Nagar *et al.,* 2011, Garima *et al.,* 2013)

NATURE	**CATEGORY**	**Example**
Natural	Carbohydrate	Sodium alginate, maltodextrins, sodium starch glycolate (SSG), pullulan, pectin.
	Resin	Polymerized rosin

Synthetic	Cellulose polymer	Methylcellulose (A3, A6, A15), carboxy methylcellulose secekol- 30, Sodium carboxy methyl cellulose, Hydroxy propyl methyl cellulose (E3, E5, E15, K3, K15, K50), Microcrystalline cellulose, Cros carrmellose sodium (CCS).
	Vinyl polymer	Poly vinyl alcohol, poly ethylene oxide, Poly vinyl pyrrolidone (K-90, K-30).
	Acrylic polymer	Eudragit (RD-100, 9, 10, 11, 12 and RL-100)

1.5.3 Plasticizers

The concentration of plasticizer, which is a crucial component in oral strip formulation, ranges from 0 to 20% by weight of dried polymer. Plasticizer aids in enhancing the films' flexibility and lowering their brittleness. Tensile strength and elongation can be increased by incorporating plasticizers. By lowering the polymer's glass transition temperature, it considerably enhances the film forming characteristics. The compatible nature of the plasticizer with the polymer and the kind of solvent used in the casting of the film will determine which plasticizer is chosen. While improper plasticizer employ can cause the film to break, shatter, and peel off the strip. Additionally, it has been suggested that some plasticizers may have an impact on how quickly a medicine is absorbed. (Siddiquinehal *et al.,* 2011, Frey *et al.,* 2006, Kulkarni *et al.,* 2002).

By lowering the polymer's glass transition temperature to between 40 and 60°C for non-aqueous solvent systems and below 75 °C for aqueous systems, plasticizer considerably enhances the strip's characteristics. Various kinds of polymers that are plasticized with several other polymers include (Pathare *et al.,* 2013). Plasticizers containing hydroxyl, such as PEG, propylene glycol, glycerol and polyols,made it simple to plasticize cellulosic hydrophilic polymers. Esters of phthalic acid and citric acid were used to plasticize less hydrophilic cellulosic polymers. Polymers like polyvinyl alcohol can be easily plasticized using glycerol. Diethylene glycol is used to plasticize films made of both hypromellose and polyvinyl alcohol. Glycerol, propylene glycol, low molecular weight polyethylene glycols, citrate derivatives such as triacetin and acetyl citrate, phthalate derivatives such as dimethyl, diethyl and dibutyl derivatives, castor oil, etc. are a few examples as shown in table 04 and 05.

TABLE 04: THE TYPE OF PLASTICIZER USED IN A FEW DRUGS (Pathare *et al.,* 2013)

Drugs used for oral thin films formulation	**Type of Plasticizer used**
Metoclopramide hydrochloride	Glycerol
Ropinirole hydrochloride	PEG-400
Montelukast Sodium	Glycerine
Amlodipine hydrochloride	Glycerol

Triclosan	Propylene Glycol
Telmisartan	Propylene glycol
Livocitrazine dihydrochloride	Glycerine, dibutyl phthalate

TABLE 05: ADVANTAGES OF PLASTICIZER WITH THEIR JUSTIFICATION (Rohini *et al* ., 2012)

Advantage of Plasticizer	**Stronger than**	**Justification**
Sorbitol	Mannitol	Since it does not crystallise during drying films
Malic acid	Oleic acid, Tartaric acid, Citric acid	Due to the fact that itdoes not crystalize after drying films
PEG-300(low molecular weight)	PEG (high molecular weight)	They created more aesthetically pleasing transparent films and had a reduced water vapour permeability rate

1.5.4 SALIVA STIMULATING AGENT

These substances are designed to enhance salivation, which aids in the oral thin film's quicker dissolution. Salivary secretions are induced through the use of tartaric acid, ascorbic acid, malic acid, and citric acid. Between 2 and 6% w/w of the strip's weight, these ingredients can be utilised singly or in combination. (Aggarwal *et al.*, 2011,Ghodake *et al* ., 2013).

1.5.5 SWEETENING AGENT

Natural sweetening agent

Sweeteners have emerged as a crucial component for pharmaceutical and nutraceutical goods whose the oral cavity is the site of product dissolution. Traditional sweeteners include sucrose, dextrose, fructose, glucose, liquid glucose, and isomaltose. Because fructose is sweeter than sorbitol and mannitol, it is a common sweetener. Polyhydric alcohols like sorbitol, mannitol, and isomaltose can be combined as they also have a pleasant mouth feel and a cooling effect. The formulation of oral medicines must take into account the fact that polyhydric alcohols are less cytotoxic and have no residual taste **(**Sau-hung *et al* ., 2003).

Artificial sweetening agent

The use of synthetic sweeteners in both food and pharmaceutical preparations has increase. Synthetic sweeteners can be divided into two groups, I generation and II generation sweeteners, as shown in the table below. Sucralose and acesulfame-K are 200–600 times sweeter

than sugar. Neotame and alitame have a sweetening capacity that is 2000–8000 times more than sucrose. Rebiana, a natural sweetener made from the south american plant stevia rebaudiana, has a 200 – 400 fold improved sweetness. (Prakash *et al* ., 2008)

The sweetening agent and their examples are listed in the table 06

TABLE 06: LIST OF SWEETENING AGENT (Subash *et al* ., 2010)

S.NO	SWEETENING AGENT	EXAMPLES OF SWEETENING AGENT
1	Natural sweetening agent	Sucrose, maltose, xylose, ribose, glucose, mannose, galactose, fructose, dextrose, partially hydrolyzed starch, or corn syrup solids
2	Artificial sweetening agent	First generation – Aspartame, saccharin and cyclamate Second generation – acesulfame-K, sucralose, alitame, neotame

1.5.6 FLAVOURING AGENT

To mask up the bitter flavour of the formulation, any USFDA approved flavour can be applied. These agents might be chosen from synthetic flavour oils and oleo resins. Herbal extract made from a variety of plant parts, including the leaves, fruit, and flowers. The sort of flavour to be used will determine how much should be utilised. Essential oils like menthol, strong mints like peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavours like lemon, orange, or sweet confectionery flavours like vanillin, chocolate, can all be used as flavours (Ghodake *et al* ., 2013, Mahajan *et al.*, 2011).

In the oral thin film formulations, flavours are preferably added up to 10% by weight. Initial flavor quality, which is noticed in just a few seconds after the product has been ingested, and the after taste of the formulation, which lasts for at least roughly 10 minutes, are the two main factors that determine whether an individual will accept an oral disintegrating or dissolving formulation. The sort of medicine to be included in the formulation will determine what flavour is chosen. (Gavaskar *et al* ., 2010) The flavouring agents are listed below the table 07.

TABLE 07: LIST OF FLAVOURING AGENT

TYPES OF FLAVOURS	EXAMPLES OF FLAVOURING AGENT
Fruity flavors	Cocoa, coffee, chocolate, vanilla and citrus
Fruit essence type	Apples, raspberry, cherry, pineapple

1.5.7 SURFACTANTS

Surfactants function in formulations as a wetting, solubilizing, or dispersing agent to swiftly release the active ingredient and dissolve the film in a matter of seconds. Tweens, benzalkonium chloride, and sodium lauryl sulphate are a few of the often utilised ones. The surfactant polaxamer 407, which is employed as a solubilizing, wetting, and dispersion agent, is one of the most significant ones (Wale *et al* ., 1994).

1.5.8 COLOURING AGENTS

FD & C colours, EU colours, natural colours, and custom pantone matching colours are just a few of the colouring chemicals that are employed. When making oral thin films, FD&C-approved colours such titanium oxide, silicon dioxide, zinc dioxide, etc. are employed in concentrations that do not exceed 1% weight/weight. (Kumar *et al* ., 2014, Rao *et al* ., 2013).

2. TECHNIQUES FOR PREPARING ORAL THI FILM: (Nehal *et al* ., 2011)

These are the preparation techniques for the quickly dissolving oral thin films are listed in figure 03:

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

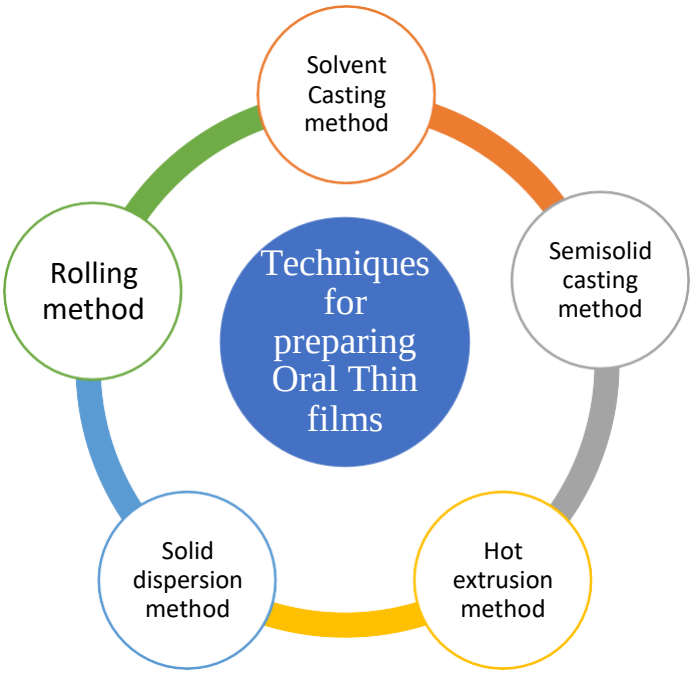

FIGURE 03: TECHNIQUES FOR PREPARING ORAL THIN FILM SOLVENT CASTING METHOD (Nehal *et a* ., 2011, Pandya *et al* ., 2013)

The solvent casting method is most frequently used to create the OTF, in which the water-soluble components are dissolved to create a transparent viscous solution. Smaller volumes of the solution are used to dissolve the API and additional agents, which are then blended with the bulk. After that, this combination is poured into the aqueous viscous solution. The vacuum removes the trapped air. The final mixture is poured into a film and allowed to dry before being cut into the required number of pieces. Cutting, stripping, and packaging are completed once the films have dried. Films can be cut into the appropriate sizes and shapes. The most widely used film sizes are 2 x 2 cm^2 and 3 x 2 cm^2.The solvent casting method equipment are shown in figure 04.

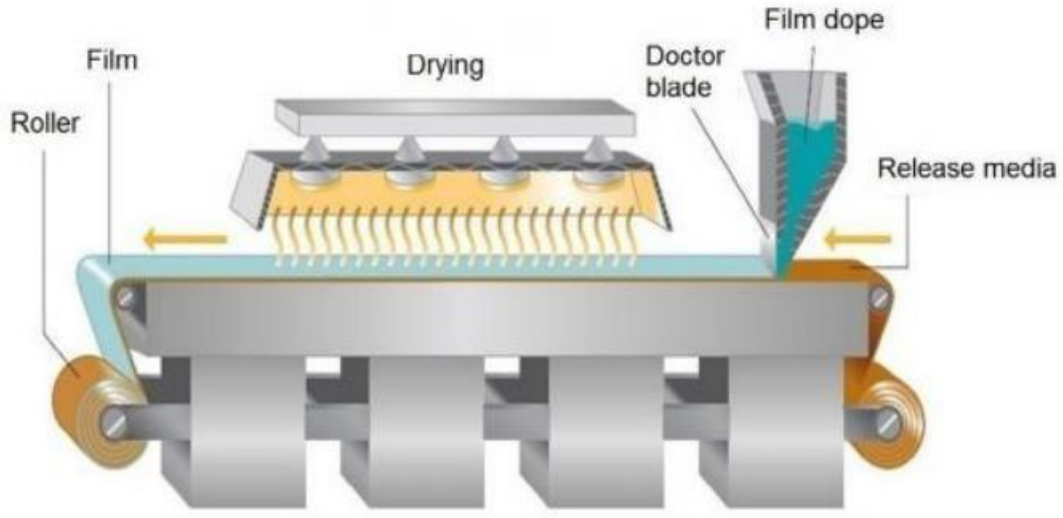

FIGURE 04: SOLVENT CASTING METHOD (Nehal *et al* ., 2011)

Advantages:

- Compared to extrusion, film has superior uniformity of thickness and better clarity
- It has an elegant shine and is devoid of flaws like die lines. It also has better physical characteristics and is more flexible
- Although different thicknesses are available to fulfill API loading and dissolution requirements, the recommended finished film thickness is typically between 12 and 100 μm.

Disadvantages:

- The polymer must be readily soluble in a volatile solvent or in water
- A solution that remains stable with a tolerable minimum solid content and viscosity should be generated.

PROCEDURE FOR SOLVENT CASTING METHOD

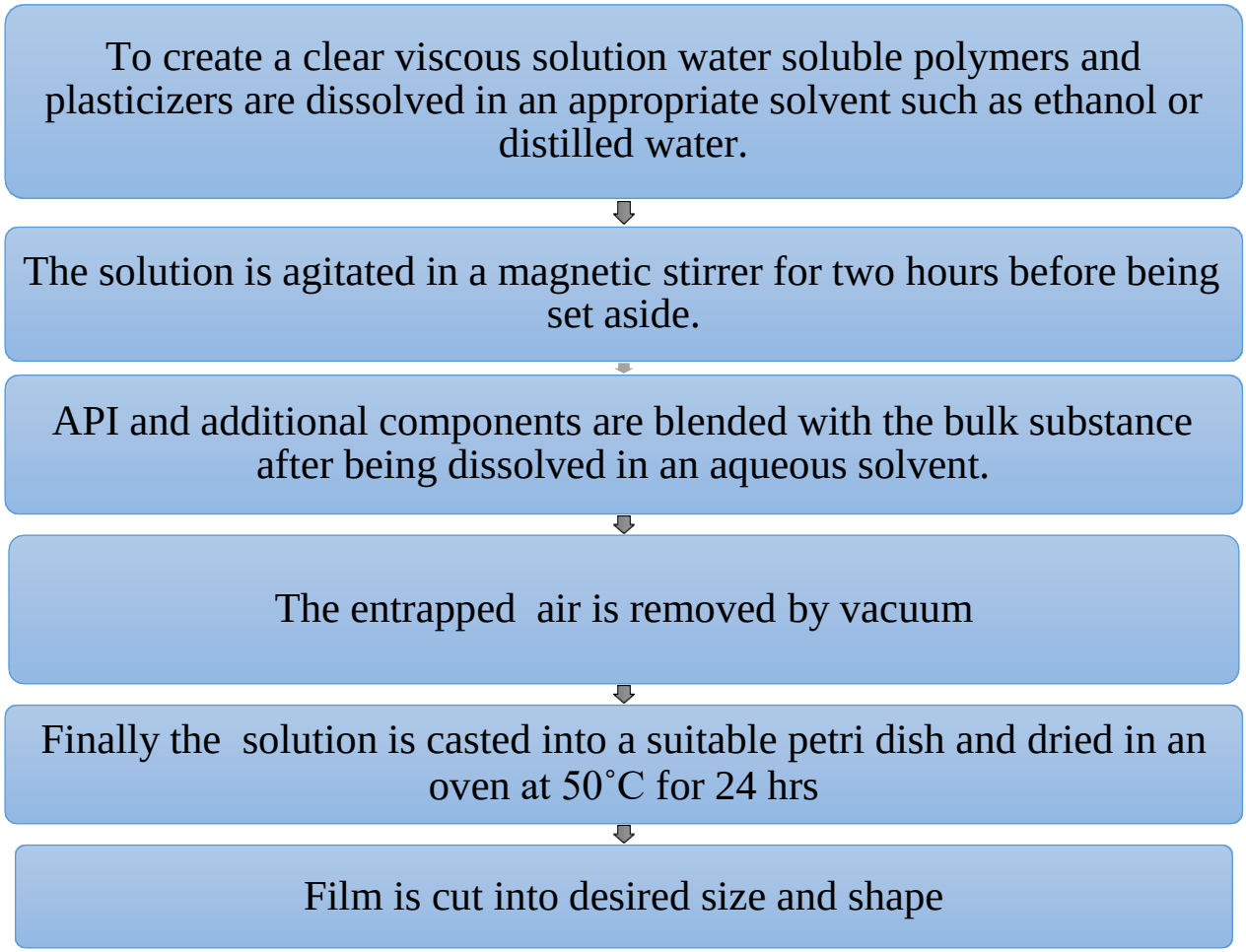

Figure 05: **PROCEDURE FOR SOLVENT CASTING METHOD**

SEMISOLID CASTING METHOD: (Nehal S *et al* ., 2011, Pandya K *et al* ., 2013)

The water-soluble film producing a polymer solution is created initially in the semisolid casting process. The resultant solution is mixed with an acid insoluble polymer solution (such as cellulose acetate phthalate or cellulose acetate butyrate), which can be made with sodium hydroxide or ammonium hydroxide. The right quantity of plasticizer is then added, resulting in the formation of a gel mass. Finally, heat controlled drums are used to cast the gel mass into the films or ribbons. The film has a thickness of between 0.015 and 0.05 inches. It is recommended to use a 1:4 ratio for the film-forming polymer with the acid-insoluble polymer.

PROCEDURE FOR SEMISOLID CASTING METHOD

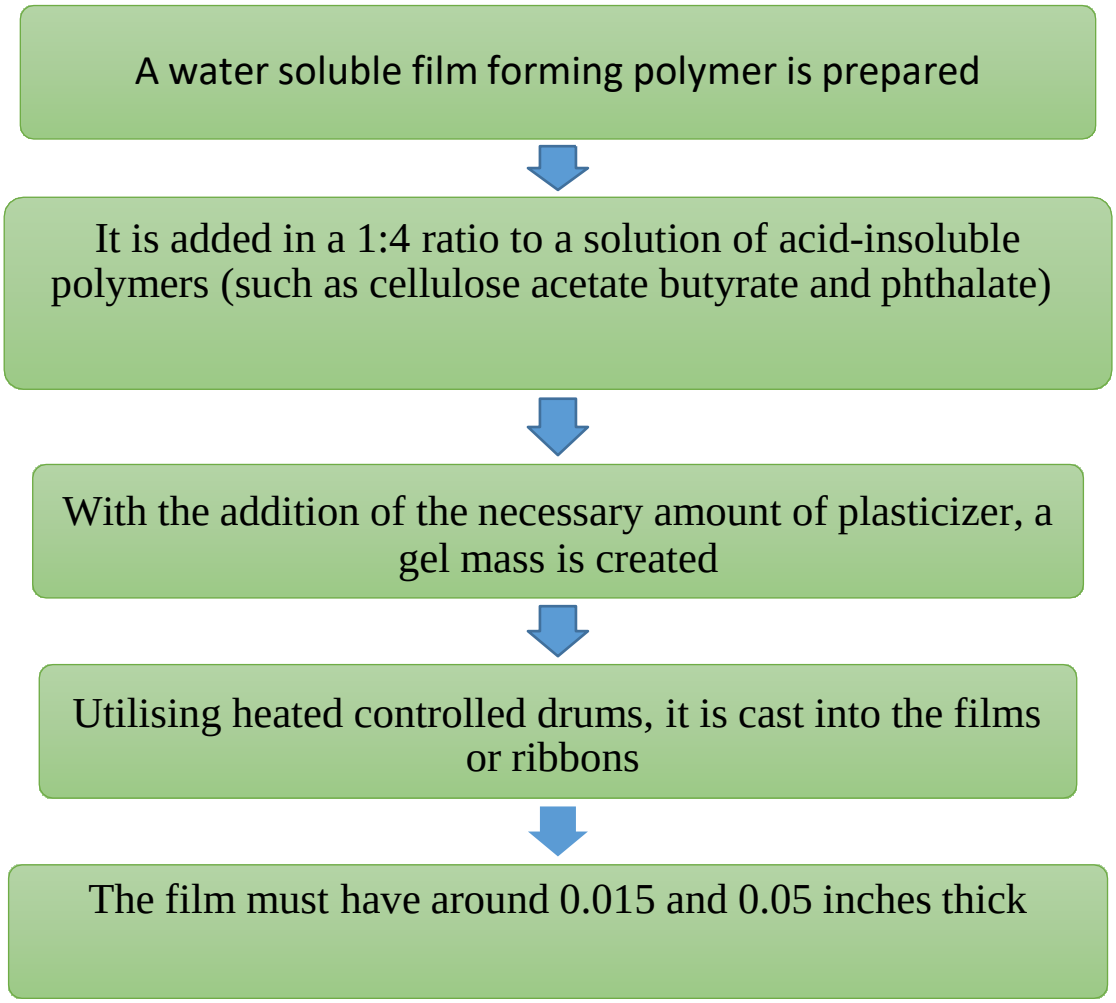

FIGURE 06: PROCEDURE FOR SEMISOLID CASTING METHOD

HOT MELT EXTRUSION METHOD: (Nehal *et al.*, 2011, Pandya *et al.*, 2013,.Naga Sowjanya Juluru .,2013, Repka *et al* .,2003)

In this process, the medication and carriers are first combined in solid form. The mixture is then melted by the extruder's heaters. The dies ultimately create the melt into films. The hot melt extrusion method equipment are shown in figure 07.

Advantage:

- ✓ The API's compressibility characteristics might not be significant
- ✓ A better substitute for medications that are poorly soluble
- ✓ Uses less energy than high-shear techniques
- ✓ Without the use of any water or solvents
- ✓ The fewer steps in the processing
- ✓ Greater uniformity of dispersion due to vigorous mixing and agitation.

DISADVANTAGE:

There are a few drawbacks to using high temperatures: thermal deterioration; flow characteristics of the polymer are crucial for processing; there are few polymers available additionally, all excipients must be free of water or any other volatile solvent.

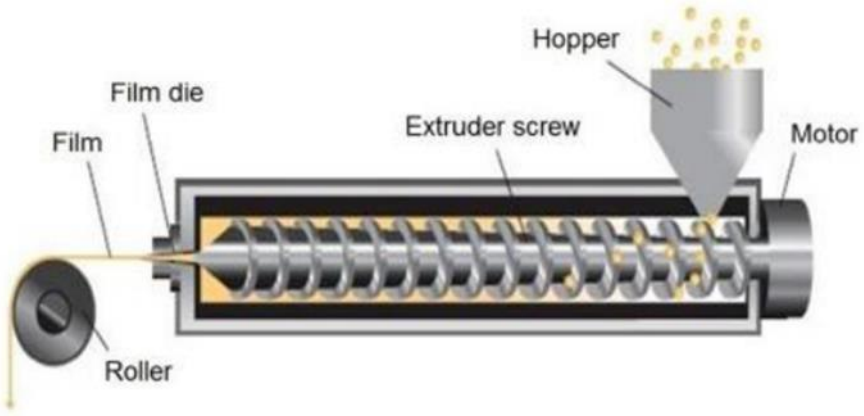

FIGURE 07: HOT MELT EXTRUSION METHOD (Nehal *et al* ., 2011)

PROCEDURE FOR HOT MELT EXTRUSION METHOD

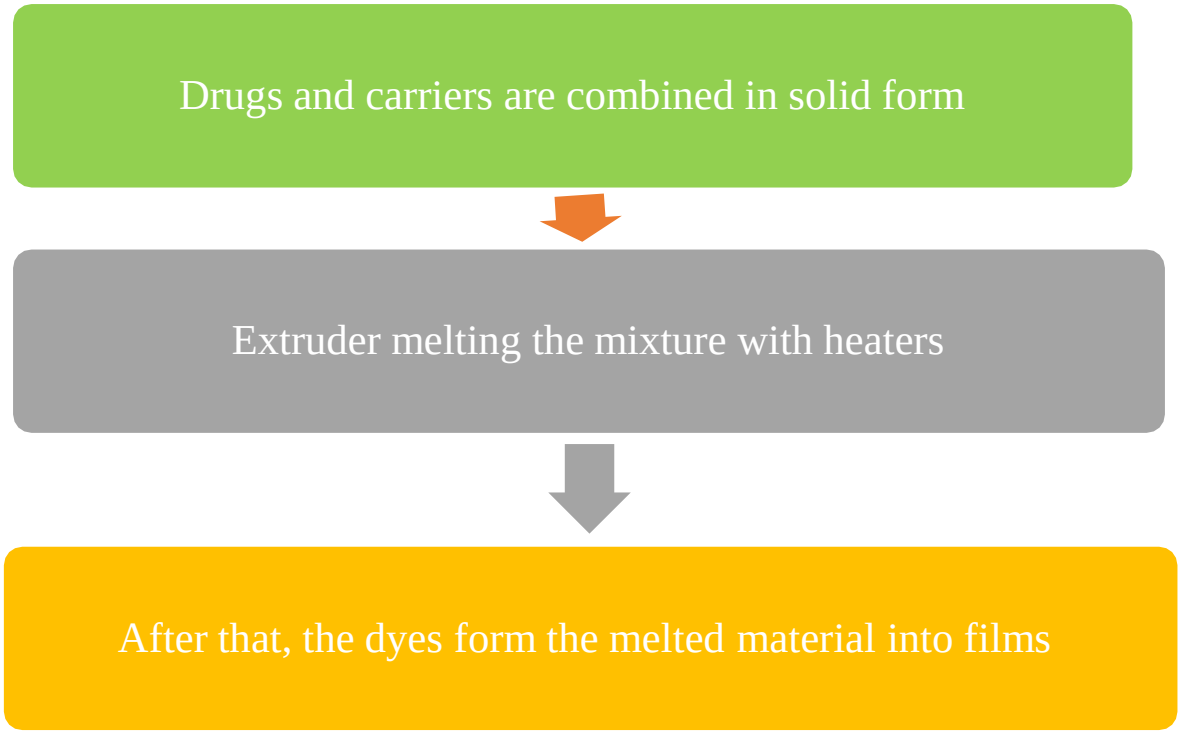

Figure 08: PROCEDURE FOR HOT MELT EXTRUSION METHOD

SOLID DISPERSION EXTRUSION METHOD (Pandya *et al*., 2013, Naga Sowjanya Juluru .,2013, Repka *et al* .,2003)

In this technique, amorphous polymers with hydrophilic characteristics are used to disperse one or more active components in an inert carrier in a solid form.

PROCEDURE FOR SOLID DISPERSION EXTRUSION METHOD

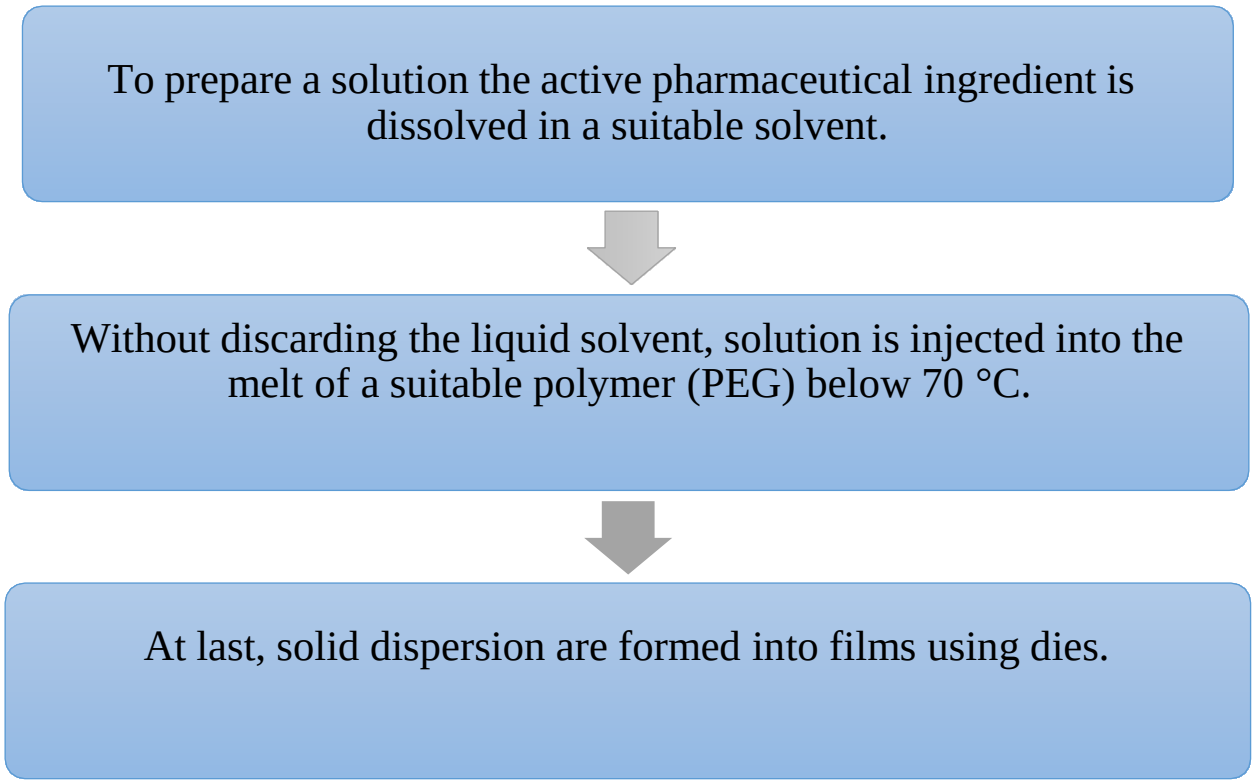

FIGURE 09: PROCEDURE FOR SOLID DISPERSION EXTRUSION METHOD

Precautions to take when making solid dispersions

When making solid dispersions, care must be taken because the chosen solvent or medication may not melt with polyethylene glycol and may modify the drug polymorphic form, which will precipitate in the solid dispersion.

ROLLING METHOD (Pallavi *et al.*, 2014, Panda *et al.*, 2012)

The rolling process typically uses water or water-alcohol combinations as the solvent. The active substance and other components are dissolved in tiny quantities of aqueous solvent by the high shear processor. A carrier roller is used to roll the viscous mixture. In order to prepare the resulting films, they are first trimmed to the required sizes, and then they are carefully dried. The equipment of rolling method are shown in figure 10 and figure 11.

ROLLING METHOD PROCEDURE

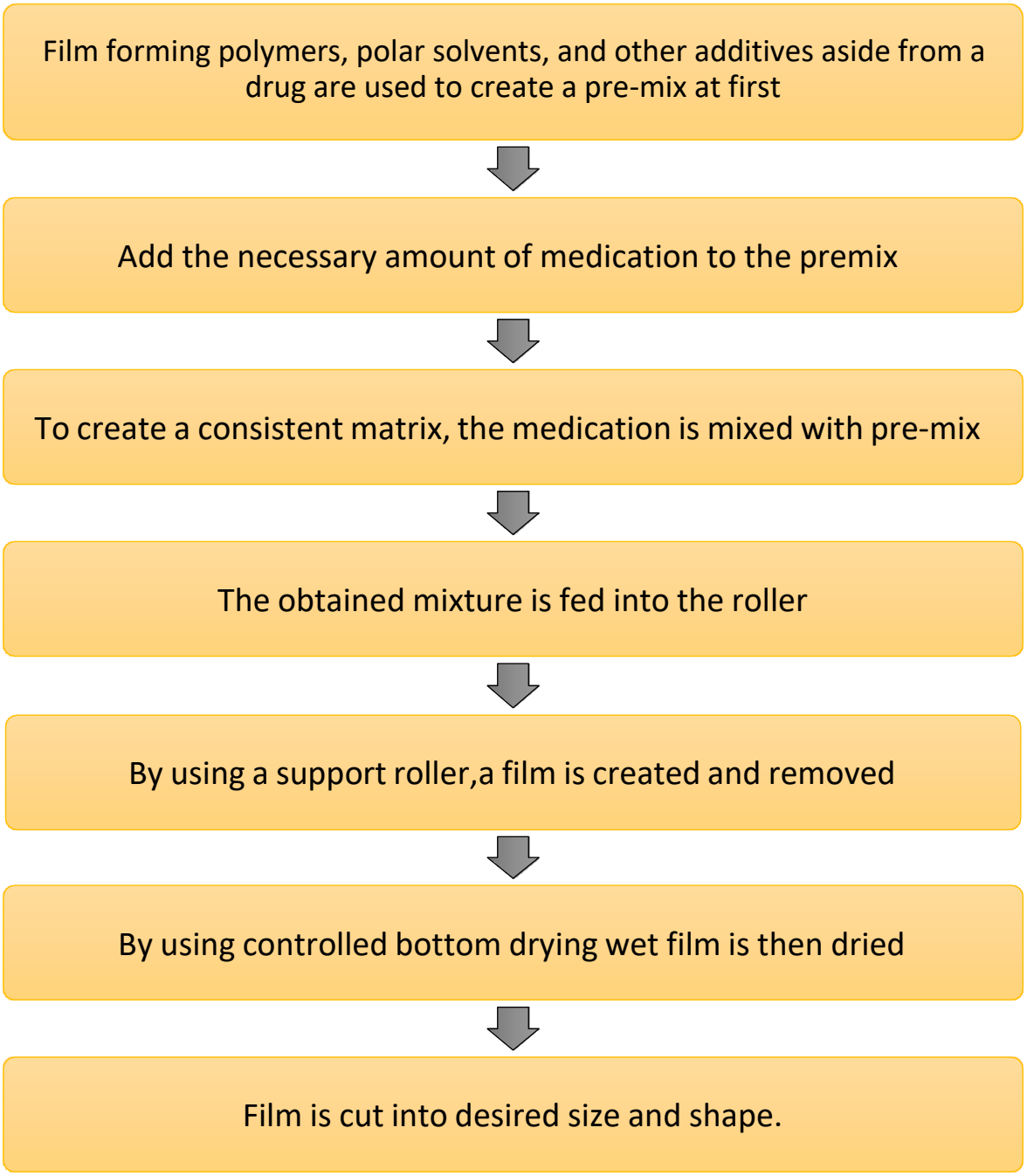

FIGURE 10: PROCEDURE FOR ROLLING METHOD

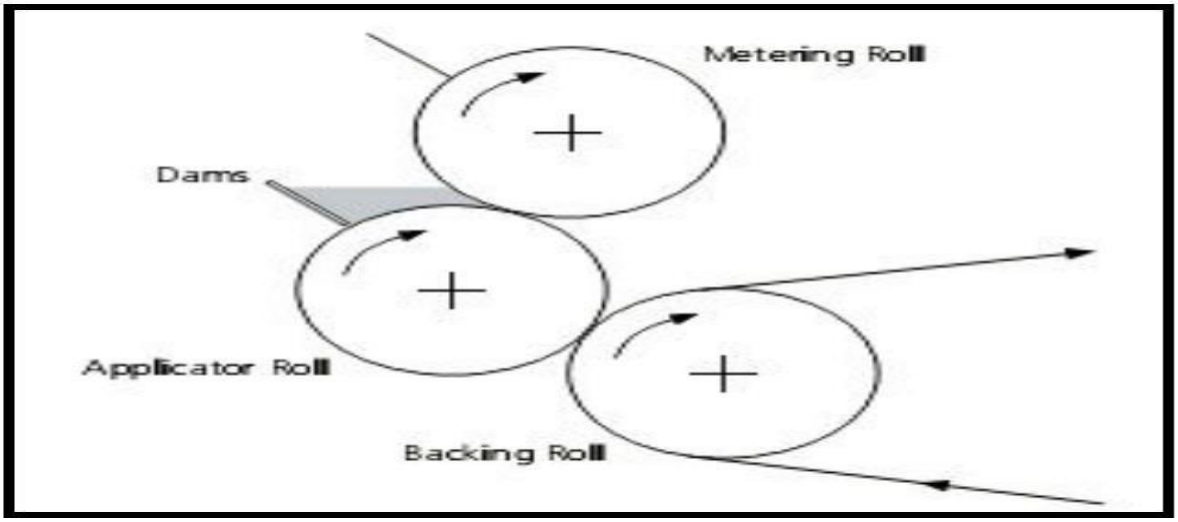

Figure 11: Rolling method (Nehal S *et al* ., 2011)

3. EVALUATION PARAMETERS

Test for thickness

The film thickness determines the drug dosing accuracy. In order to determine the ultimate thickness of the film, it is measured using a calibrated digital vernier callipers or micrometer screw gauge at five separate crucial places. The mean value is then determined. The ideal range for the film thickness is 5-200 µm. (Rathi *et al.*, 2011, Kumar *et al.*, 2013).

Test for dryness / tack

Tack is the tenacious with which a strip clings to an object, such as a sheet of paper, after being rubbed against it. Set to touch, dust free, tack free, dry to touch, dry hard, dry through (dry to handle), dry to recoat, and dry print free are the eight phases of the drying process for films. This test can be done with a variety of tools. (Dixit *et al.*, 2009).

Tensile strength

Tensile strength is the amount of stress that can be applied to a strip specimen before it breaks. The formula used to calculate it is as follows (Patil *et al* ., 2014)

Tensile strength = Load at failure × 100/Strip thickness × Strip width.

Tear Resistance

The ability of a synthetic film or strip to withstand tears is a complex function of the material's overall resistance to rupture. Additionally, a maximum resistance is necessary to rip the film. 51 mm/min is a very low rate of load. The force is measured in Newtons or pounds. **(**Thakur *et al* ., 2013).

Folding endurance test

The folding endurance test reveals the film's brittleness. The method for determining it involves repeatedly folding the film in the same spot until the film breaks. The folding endurance value is determined by counting the amount of times the film folded without tearing (Kumar *et al* ., 2013, Ahmed *et al* .,2009).

Moisture absorption capacity

This test was used to determine whether the films would remain stable and intact under highly humid conditions. A film was placed within a desiccator filled with a typical aluminium chloride solution to maintain the humidity level at 79.55% relative humidity. After three days, films were taken, and their % of moisture absorption was determined by weighing them. (Ahmed *et al* .,2009).

% Moisture content = (Initial Weight-Final weight)/(Initial weight) × 100

Percentage Elongation

Strain is the stretching that occurs when stress is applied to a strip sample. Strain is essentially the strip's distortion divided by the sample initial dimension. It is directly influenced by the plasticizer used. As plasticizing agent content rises, it rises. (Jaiswal *et al.*, 2014).

% Elongation = Increase in length of the film ×100 / Initial length of film

Young's Modulus

This term refers to the strip's stiffness. In the zone of elastic deformation, it is the ratio of applied stress to strain. The tensile strength and young's modulus of hard, brittle films are high. (Gowri *et al.,* 2014, Rajini *et al.,* 2013).

Young's modulus = Slope × 100 /Strip thickness cross × head speed

Disintegration test

The duration (in seconds) during which a film disperses after coming into touch with saliva or water is referred to as the disintegration period. The thin film starts to break up or disperse at the disintegration moment. The physical characteristics of water-soluble films are greatly influenced by the weight and thickness of the film (Malke *et al.,* 2009). The disintegration periods of OTFs can also be ascertained using the disintegration test equipment recommended by pharmacopoeias. The disintegration duration of the film composition typically ranges from 5 to 30 seconds, and it depends on the formulation content. There is no formal method to determine how quickly a film will disintegrate (Irfan et al., 2016).

Dissolution rate test

Several studies in the literature improvised the dissolution rate testing apparatus while others employed franz diffusion cells to assess drug release from polymeric films. (Adrover A *et al.,* 2015). Placing the film specimens is the biggest challenge in the dissolution rate assay. Additionally, a number of techniques have been used in the literature in which a double-sided adhesive band is used to attach the film dissolution rate to the base of a glass container or a mixing device.

Testing for Stability

Accelerated stability research is carried out under typical stress conditions, such as humidity, light, and tempeature. For 4–24 weeks, a piece of film was kept in an aluminium box at 25°C with 50–60% humidity or at 40°C with 75–80% humidity. The drug content was then determined. (Jaiswal *et al* ., 2014,Kaushal *et al* ., 2013, Shweta *et al* .,2012,Kulkarni *et al.,* 2010)

Content uniformity

Estimating the API content of each individual strip yields information about content homogeneity. 85-115 % is the content uniformity maximum (Jaiswal *et al* ., 2014).

Swelling properties

Each film sample is weighed before being placed in a stainless steel wire mesh that has already been pre-weighed to evaluate its swelling qualities. In a plastic container with 15 ml of medium, the mesh-containing film is immersed until a steady weight is noticed, the increase in film weight is measured at various time intervals. Equation (Bhyan *et al.*, 2011, Khairnar *et al* ., 2009, Deshmane *et al* ., 2010) as used to calculate the degree of swelling.

% Swelling degree = (Final weight – Initial weight) × 100/(Initial weight)

Determination of pH value

Determining the pH of oral thin films is crucial for understanding their dispersion/solubility in the mouth, taste characteristics, and fast drug release. 1.5% – 2% (w/v) agar is dissolved in the isotonic solution and added for this reason. This mixture is then put in to a petri dish and allowed to sit there until it cools enough to gel. On it, oral thin film samples are positioned. The pH of pH sheets with a range of 1 to 11 is then calculated by touching themto oral thin films and seeing how the colour of the paper changes (Kathpalia H*et al* ., 2013, Jelvehgari M*et al* ., 2015).

Transparency

A basic UV spectrophotometer can be used to gauge the film transparency. Rectangles cut from the film sample were positioned on the inside of the cell's spectrophotometer at 600 nm the film transmittance is assessed (Bhyan *et al* ., 2011).

- Transparency = logT600/b

Where T600 = Transmittance at 600nm

b= Film thickness (mm)

Contact Angle

At ambient temperature, a goniometer is used to quantify contact. Put a drop of purified water on the dried film surface. Within 10 seconds after a water drop deposition, images of the drop were captured using a digital camera. On both sides of the descent, the angle of contact was measured, and the average was determined as shown in figure 12 (Saini *et al* ., 2012).

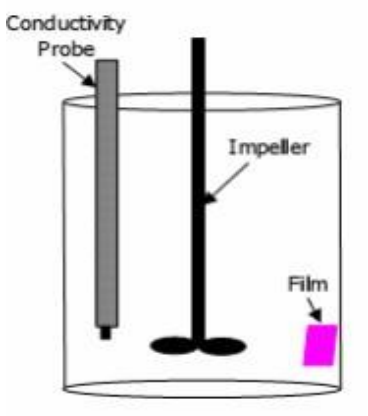

Figure 12: Diagram of contact angle equipment set up (Bettini R *et al., 2008)*

Morphological and organoleptic control

The Oral thin films are sensually and aesthetically assessed for their colour, uniformity transparency, fragrance, and texture. Particular attention should be paid to their flavour and flavour characteristics (Senthilkumar *et al.,* 2015, Jelvehgari *et al .,* 2015).

Packaging

There are several different ways to package fast dissolving film systems, including individual packages, multiple blister packages, and multi-unit rolls. Currently, the pharmaceutical industry has a few patented packaging solutions for oral thin films (Siddiqui *et al.,* 2011).

4. MARKETED FORMULATION

A few of the commercially available formulas using oral thin film technology are listed in table 08 (Nishi Thakur *et al ., 2013).*

Table 08: Marketed formulation of oral thin film

Product	**Uses**	**API**	**Manufacturer**
Triaminic	Antiallergic	Diphenhydramine	Novartis
Gas-X	Antiflatuating	Simethicone	Novartis
Theraflu	Antiallergic	Dextormethorphan	Novartis
Klonopin wafers	Antianxiety	Clonazepam	Solvay pharmaceuticals
Benadryl	Antiallergic	Diphenyhydramine HCL	Pfizer
Suppress	Cough suppressants	Menthol	InnoZen ,Inc
Sudafed PE	Congestion	Phenylepinephrine	Novartis
Listerine	Mouth ulcer	Cool mint	Pfizer ,Inc .
Orajel	Mouth freshner	Menthol/Pectin	Del
Chloraseptic	Sore throat	Benzocain/menthol	Wolters Kluwer Health , ,Inc .

5. Conclusion

The majority of pharmaceutical businesses in this industry are continuing their research and development efforts to adapt their products in various categories to this technology as oral thin films have emerged as a revolutionary trend. This technique is a cutting edge method of medicine delivery for all patient populations with swallowing issues, but particularly for young children and elderly people. Additionally, it has various benefits over other dose forms, including better absorption and quicker results. It is one of the most significant dosage forms that can be taken orally when an instant effect is sought or in emergency situations. Therefore, it can be said that oral thin films have unique future potential together with high patient compliance and many benefits.

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