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FORMULATION AND EVALUATION OF ORAL DISSOLVING FILMS

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ABSTARCT

The pharmaceutical companies are looking for novel ways to distribute drugs, and one such way is through oral films. It has been said that oral films offer an alternative to traditional dose forms. They offer rapid, local, or systemic effects and are a very flexible platform. Furthermore, patients with dysphagia, elderly, pediatric, or bedridden patients, as well as those who have difficulty accessing water, can simply utilize these devices on their own. There are several ways to administer this drug delivery system, including transdermally, ocularly, buccally, sublingually, and orally. These review looks at oral dissolving films from a modern perspective and provides insight into the industry's expanding global market share as a result of expanding research areas and technological advancements. Simultaneously, it offers a summary of the crucial elements linked to formulation design that impact oral film technology, such as oral film design, physiological and auatomical constraints, appropriate manufacturing process selection, characterization methods, and the physicochemical characteristics of drugs and polymers. It also offers information on the most recent oral film products that different pharmaceutical companies have developed.

Keywords: Oral Dissolving Film (ODF), Drug Delivery Systems, Pharmaceutical Sector, Polymers, Fast Dissolving, Bioavailability.

I. INTRODUCTION

Oral film technology was initially developed in the late 1970s to help paediatric and elderly patients who had trouble swallowing tablets and capsules. Today, it is popular in the pharmaceutical industry because it is less fragile than other oral dosage forms. [1,2] One of the most popular methods for administering medication is orally since it is more affordable, convenient, and easy to administer, all of which increase patient compliance.[3]

A novel medication delivery method for oral administration of medications is the oral fast dissolving film. Since oral drug delivery is thought to be the most patient compliant, convenient, safe, and cost-effective way of drug delivery, almost 90% of medications used to treat various disorders and diseases are given to the body through this route. [4-7]

When applied to the tongue or buccal cavity, fast dissolving oral thin films, an ultra-thin film, use a hydrophilic polymer that quickly hydrates or sticks.[8] Without drinking or chewing, these films breakdown or disintegrate in a matter of seconds to release the active ingredient. [9,10] Bypassing first pass metabolism produces the rapid bioavailability. For this reason, they are typically made for medications with high first-pass metabolism in order to increase bioavailability. [11,12]

OTFs are also known to have a shelf life of two to three, depending on the API, but they are quite susceptible to moisture in the environment.[13]

The films are made to disintegrate in a matter of seconds when they come into touch with a moist surface, such the tongue, so users can eat the product without adding more liquid. This ease-of-use boosts patient compliance while also offering a marketing benefit. Since the medication enters the bloodstream directly, first pass effects and gastrointestinal tract deterioration are prevented. Because of these features, this formulation is the most well-liked and accepted among older and paediatric patients as well as those who are afraid of choking. [14,15,16]

These days, oral thin films are a tried-and-true method for systemic distribution of active pharmaceutical ingredients (APIs) for prescription and over-the-counter (OTC) pharmaceuticals.[17]

Based on the technology of the transdermal patch, fast dissolving films are a kind of oral drug delivery device for the oral distribution of the medicine. The delivery system consists of a thin film that is applied to the patient's tongue or mucosal tissue and immediately moistened by saliva. The film then quickly breaks and disintegrates, releasing the drug for absorption through the oral mucosa. [18,19]

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Hydrophilic polymers are used to make fast- dissolving oral films, which disintegrate quickly on the tongue or in the buccal cavity and release the medication into the bloodstream when they come into contact with liquid. Fast-dissolving oral film has become a sophisticated substitute for the conventional pills, capsules, and liquids that are frequently connected to over-the-counter and prescription drugs. Thin-film strips, which resemble a postage stamp in size, shape, and thickness, are usually intended for oral administration. The user places the strip on the inside of the cheek or beneath the tongue (sublingually).

With these drug delivery methods, the medication can avoid going through the first pass metabolism, increasing its bioavailability. Through enteric, buccal, or sublingual routes, the medication can reach the bloodstream when the mouth thin film dissolves. [20,21]

In addition to increasing the drug's aqueous solubility, one of the primary challenges of the current study was taste masking because all medications that enter the oral cavity by swallowing, sublingual application, or oral inhalation should taste good. The bad taste of the active pharmaceutical ingredients (APIs) in these dosage forms has been found to be one of the main obstacles preventing patients from following a prescribed treatment schedule. In terms of patient acceptance and compliance, taste plays a significant role in the creation of oral medications. It is oral formulations, particularly in pediatric medicine. [22,23,24]

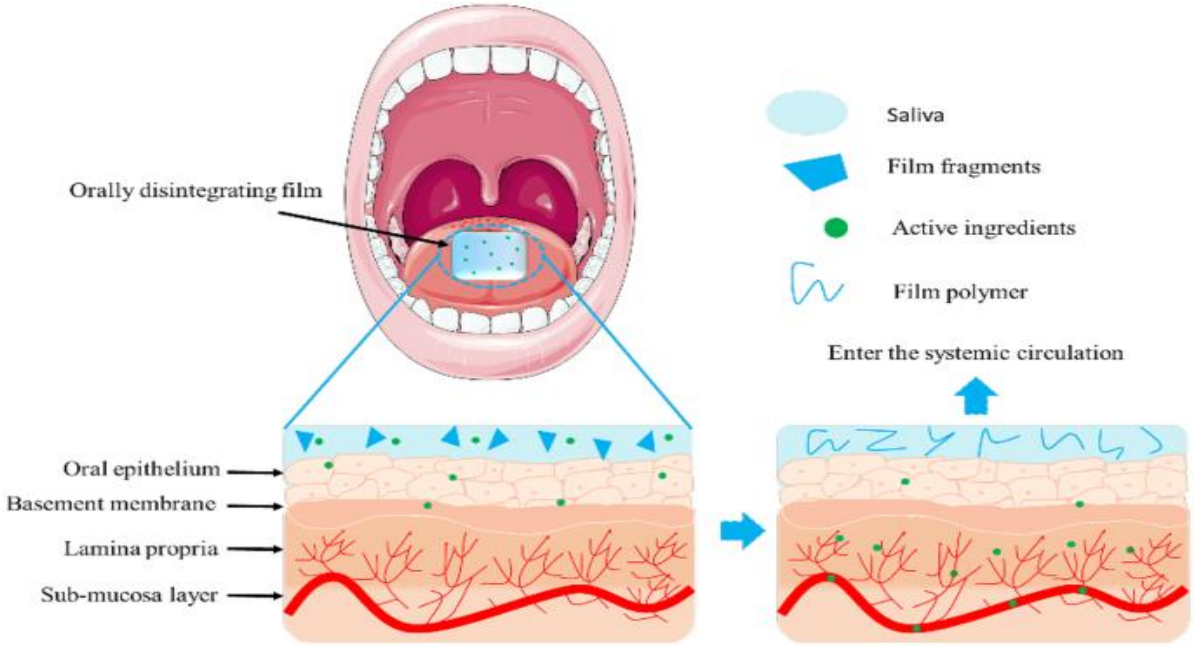

Figure 1: Oral dissolving film

II. METHODOLOGY

COMPLEXATION:

Complexation is the reversible affiliation of two or more molecules, resulting in a nonbonded entity with determined stoichiometry. Complexation relies on weak forces such as Vander Waals, hydrogen bonding, and hydrophobic interactions.

Inclusion Complexes – Cyclodextrins:

Cyclodextrin dextrin inclusion complexes are produced by inserting a non polar molecules or area into the cavity of another molecule or group of molecules. Cyclodextrins are the most widely employed host molecules. CDs are α-1,4-linked oligosaccharides of α-D-glucopyranose, with a hydrophobic core cavity and hydrophilic outside surface. CD's are α-1,4- linked oligosaccharides of α-D-glucopyranose, with a hydrophobic core cavity and hydrophilic outside surface. CD's hydrophobic cavity traps various molecules, resulting in inclusioncomplex. The CD molecules are toroidal or cone-shaped, as illustrated in figure1. CD and its derivatives have gained popularity in the pharmaceutical industry for their ability to build complexes with various therapeutic molecules over the last two decades. CDs boost the solubility of water-insoluble drugs by forming inclusion complexes. Drugs complexed with CD have numerous benefits, including increased solubility, better

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bioavailability, stability, and masking of natural α, β and γ CDs include six, seven, and eight units of Glucose, resulting in less volatility, reduced side effects, and potential for drug release systems. The α-CD has the smallest hollow (inside diameter of nearly 5A°) β-CD and γ-CD are ideal or pharmaceutical technologies due to their larder cavity sizes. (Internal diameter are approximately 6°and 8°respectively).[25,26]

β-Cyclodextrin

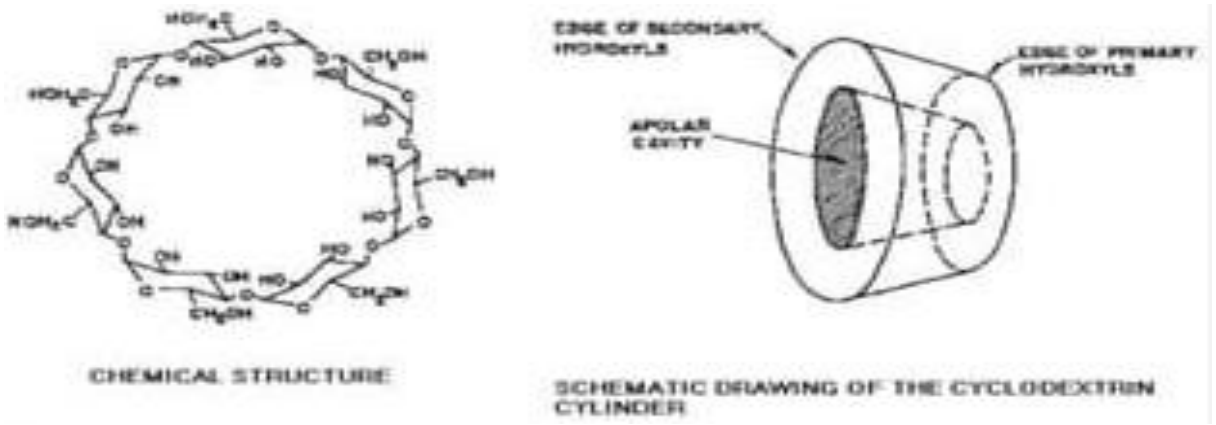

Figure 2: Representation of CD as truncated cone

Complexation Techniques many processes are employed to create cyclodextrin complexes, including grinding, kneading, co-operation, solid dispersion, neutralization, spray drying, freeze drying, melting, and more. The name itself refers to the process of complex creation.

1. Physical blending / Grinding method:

Inclusion complex can be created by simply grinding / triturating the medication with cyclodextrin in a mortar on a modest scale. On a large scale, complexes are prepared by extensively combining the medication with cyclodextrin in a fast mass granulator for around 30 minutes.

2. Kneading method:

A cyclodextrin paste is made with a tiny amount of water and the medicine is mixed in without a solvent or with a small amount of ethanol. After grinding the paste, the solvent evaporates and a powder-like complex is created. On a laboratory scale, kneading can be accomplished with a mortar and pestle. On a big scale, kneading can be done with extruders and other machinery. Parikh (Parikh et al., 2005) observed that the complexation approach improved the solubility of Nimesulide.

3. Co-precipitation:

Dissolve cyclodextrin in water, then add the guest while agitating the solution. If the visitor can withstand the increased temperature, heating allows for the dissolution of additional cyclodextrin (20%). To generate a precipitate, the cyclodextrin and guest solution must be chilled while stirring. Decant, centrifuge, or filter the precipitate and wash it. Mehramizi (Mehramizi A et al.1977) investigated the solid-state characterization and dissolving properties of GliclazideBeta- cyclodextrin inclusion complexes.

4. Solid dispersion / co-evaporated dispersion:

This approach involves dissolving the medication and cyclodextrin in ethanol and water separately. Both solutions are mixed and agitated to achieve equilibrium. The resultant solution is evaporated to dryness, preferably under vacuum.

5. Melting:

To prepare complexes, just melt the guest and combine it with finely powdered cyclodextrin. In such instances, there should be a significant excess of guest, which is eliminated after cooling by carefully washing with a weak complex, forming solvent, or vacuum sublimation (Pandya SJ et al 2008).

6. Spray drying:

A suitable solvent is used to generate a first monophasic solution of the medication and cyclodextrin. The solution is then agitated equilibrium, after which the solvent is removed by spray drying. Vozone (vozone CM, et

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at. 2003) discovered budesonide complexation in cyclodextrins, as well as particle aerodynamic characterization of the complex solid from for dry powder inhalation.

7. Lyophilization / Freeze drying technique:

Lyophilization / freeze drying is a suitable method for producing a porous, amorphous powder with a high degree of contact between the medication and the cyclodextrin. The solvent system is removed from the solution using a primary freezing and subsequent drying of the solution containing both Drug and cyclodextrin under lowered pressure. This process successfully converts thermolabile compounds into complex forms.

8. Neutralization method:

Separately dissolve the drug and cyclodextrin in 01 N sodium hydroxide, mix and agitate for about half an hour, record the pH, and add 0.1 N HCL dropwise with stirring until the pH reaches7.5, at which point complexes precipitate. The residue is filtered, and Review Article ISSN 2277-8713 Rajendrakumar A. IJPRBS, 2013; volume 2(2): 291-304. IJPRBS is available online at www.ijprbs.com. Washed until chlorine -free. It is dried at 2500C for 24 hours and kept in desiccators. Duchhene (Duchhene D et al 2007) investigated the improvement of piroxicam solubility via complexation with betacyclodextrin.[27]

FORMULATION:

Fine films that are five to twenty centimeters in diameter and contain substances that are matrix-victimization shaped are swiftly dissolved by ODFs. Use of the alternative excipient, e.g. Plasticizers, colorants, sweeteners, taste agent for masking, etc. Potent component of medications total up to fifteen milligrams. Softener strengthens and spreads the film and resilience, raising the transitional glass temperature of polymers.[28]

General composition of ODF:

Table 1: General composition of ODF

Ingredients	Concentration (%)
API (drug)	01-25
Plasticizer	00-20
Flavoring agents	02-10
Sweetening agents	03-06
Hydrophilic polymer/film former	40-50
Saliva stimulating agent	02-06
Color	01
Surface active agent	Quantity required

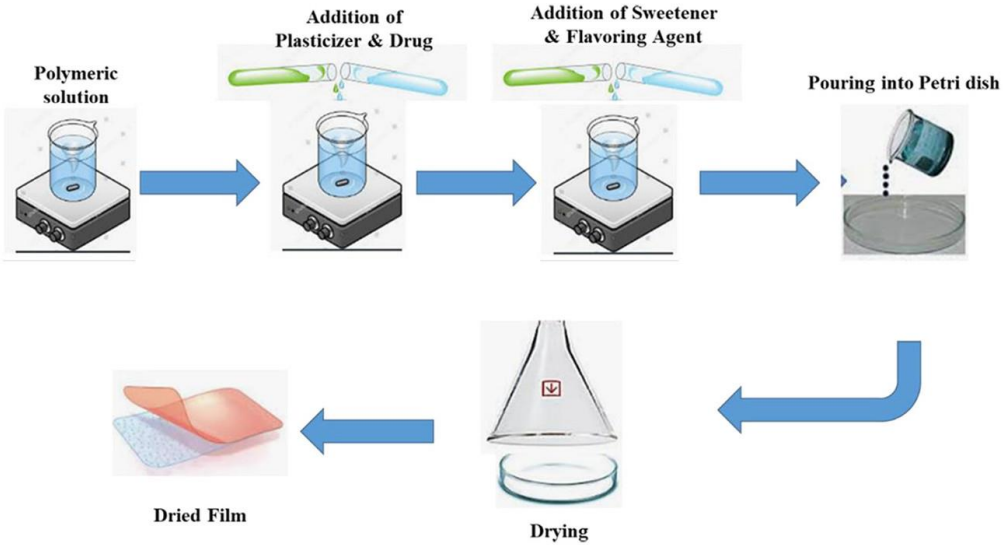

Figure 3: General process for the formulation of oral dissolving films

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1. Drug:

Several pharmacological classes, such as Anti-ulcers (like Omeprazole), Anti-asthamatics (like salbutamol sulfate), Anti-tussives, expectorants, Anti-histaminics, and NSADIs (like Dexamethacone, salbutamol, and Diacerin, Ondansterone), can be developed as mouth dissolving films. [29,30,31]

2. Hydrophilic polymers:

Film formers are made of water-soluble polymers. In medical and nutraceutical applications, the use of film forming polymers in dissolvable films has garnered a great deal of interest. The films quick disintegration, pleasant mouthfeel, and mechanical qualities are all made possible by the water-soluble polymers. By raising the molecular weight of the polymer film base, the rate of polymer disintegration is slowed down. Pullulan, Hydroxypropylcellulose, Polyvinyl alcohol, HPMC E-3 and K-3, Methyl cellulose A-3, A-6 and A-15, and maltodextrin are a few examples of water-soluble polymers used as film formers.

3. Plasticizers:

It has been found that formulation factors (plasticizers, etc.) have a significant impact on the mechanical properties of films. The use of plasticizers has also enhanced the mechanical characteristics of the films, such as tensile strength and elongation. These attributes could be impacted by variations in their concentration. Plasticizers like glycerol, di-butylphthallate, and polyethylene glycols are frequently utilized.

4. Surface active agents:

Surfactants are employed as solubilizing, wetting, or dispersion agents to breakdown films quickly and release active ingredients right away. Among the frequently utilized are tweens, sodium lauryl sulfate, benzalkonium chloride, and bezthonium chloride. Poloxamer 407, a surfactant utilized as a solubilizing, wetting, and dispersion agent, is one of the most significant surfactants.

5. Flavouring agents:

You can add any taste, including strong mint, acidic citrus, or sweet confectionary flavours.

6. Color:

There is a wide variety of colors to choose from, including FD&C, EU, Natural and custom colors that match pantones.

7. Saliva Stimulating agents:

To improve the disintegration and provide a quick release, several saliva-stimulating chemicals may also be included. Citric acid, tartaric acid, malic acid, ascorbic acid, and succinic acid are a few of these agents.

8. Sweetening agents:

The goal of the sweeteners is for them to melt or dissolve in the mouth. All sweeteners, artificial and natural, are employed in the preparation of ODFs. There seems to be two hundred metallic elements in sweetening sweeter than sugar by three to five hundred times. Rumor has it that sweeteners and aromatic compounds together have no effect on the film's elasticity.

ADVANTAGES [32-40]

1. Convenient transit
2. water is not required for administration
3. Drugs with first pass metabolism have an alternative route thanks to oral strip technology.[41]
4. Easy way to give films to people with dysphagia, recurrent vomiting, motion sickness, and mental health issues
5. Quick dissolution and disintegration in the oral cavity are made possible by the large surface area
6. films are more physically superior and have greater flexibility
7. In contrast to a tablet, the action starts quickly
8. No chance of chocking
9. concealing taste
10. local and site-specific actions

DISADVANTAGES

1. Medications that are unstable at buccal pH cannot be given

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2. This method cannot be used to give medications that irritate the mucosa
3. Because it is delicate and needs to be kept dry, it needs to be packaged carefully
4. The polymer needs to dissolve in water or a volatile solvent
5. The stable solution ought to develop, possessing a suitable minimum solid concentration and viscosity
6. Special packaging is needed to ensure the stability and safety of the product
7. It takes in moisture from the surrounding air
8. The inability to incorporate a high dose onto strip is the drawback of OS. It is recommended to use a dose of 1-30 mg.
9. Achieving dose consistency with these dosage forms presents another technological issue.

IDEAL PROPERTIES [42]

1. The medication should taste good.
2. A low dose of up to 40 mg should be used for the medicine to be assimilated.
3. The medication's molecular weight ought to be little and lower.
4. The medication must to be well-stabilized and soluble in both water and saliva.
5. At the pH of the oral cavity, it ought to be largely unionized.
6. It need to be able to penetrate the mucosal tissue of the mouth.
7. It should be lightweight, flexible, and easy to handle.
8. The films should be portable, not sticky, and maintain a flat shape without sagging.
9. The breaking down time should be as quick as is reasonable given the circumstances.
10. The surface of the film should be uniformly smooth.

CLASSIFICATION [43]

For ease of description, fast dissolve technologies can be divided in to three different groups.

- Lyophilized systems.
- Compressed tablets- based systems.
- ODF.

Lyophilized systems

Among them, this system has shown to be the most successful in terms of sales volume, value, and number of global products approvals. The technology underlying these systems forms tablet- shaped units by combining a medication suspension or solution with additional structural excipients and using a mould or blister pack. After that, the tablets or units are frozen and lyophilized inside the mould or pack. Due to their extremely high porosity, the resultant units dissolve and absorb water or saliva very quickly. Whether the active components in these systems are soluble or insoluble pharmaceuticals affects their dose handling capability; the former has a little lower dose capability than some tablet-based system systems. Compared to tablet-based systems, the units dissolve more quickly and can incorporate a variety of taste-masked components.

Compressed tablet-based systems

The production of this system involves the direct compression of excipients with ordinary tablet technology. The hardness and friability of tablet technology vary depending on the manufacturing process. This leads to a range of packaging requirements and disintegration performance, from ordinary high-density polyethylene (HDPE) bottles or blister to more specialized pack designs for product protection, such as those made by CIMA labs and PackSoly. When creating fast dissolving tablets, water soluble excipients, superdisintegrate, or effervescent components are used to enable quick water penetration into the tablet core, resulting in a faster rate of disintegration than conventional tablets. This strategy's lone deviation for tablets is Fuisz Biovail technology.[44] It makes drug-loaded candy floss with the patented shearform method, which is then tableted with other excipients. Theoretically, reasonably high dosage of medication material, including coated particles with flavour masks, can be accommodated by these devices. They may dissolve more slowly than thin-film or lyophilized dose forms, which could be a drawback. Some technological businesses, branded companies, and generic pharmaceutical companies are using the loose compression tablet technique more frequently for in-house line expansion and generic fast-dissolving dosage form development.

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ODF

A collection of flat films that are inserted into the oral cavity are known as oral films or, in related literature, oral wafers. The third type, oral film systems, has been around for a while, but in terms of fast-dissolve pharmaceutical drug delivery, they are currently of particular interest. Over the past few years, dissolveable ODF or OS has changed from the confection and dental care industries as breath strips to become a unique and extensively used recognized method for providing vitamins and personal hygiene items by customers. Businesses that had previously developed polymer coatings with active pharmaceutical ingredients (APIs) for transdermal medication delivery seized the chance to transfer this expertise to ODF forms. ODFs are now in the early to mid-development stages for prescription pharmaceuticals and are a tried-and-true method for systemic administration of APIs for over-the-counter (ODC) treatments.

TYPES OF ORAL DISSOLVING FILMS:

ODFs are classified into 3 types [45]

- Flash release
- Mucoadhesive Melt Away Wafers
- Mucoadhesive sustained release Wafers

The following table presents the properties that differentiate the aforementioned types of ODFs:

Table 2: Types of ODFs along with its properties

Properties	Flash Release	Mucoadhesive Melt Away Wafers	Mucoadhesive Sustained Release Wafers
Area	2-8	2-7	2-4
Thickness	20-70	50-500	50-250
Structure	Single layer	Single or Multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble Hydrophilic polymer	Low/non -soluble polymers
Drug Phase	Solid Solution	Solid Solution or Suspended Drug Particles	Suspension and/ or solid solution
Application	Tongue	Gingival or Buccal region	Gingival or other suitable region in the oral cavity
Dissolution	60s	In few minutes forming Gel	Maximum 8-10 h
Site of Action	Systemic or local	Systemic or local	Systemic or Local

METHODS APPLIED IN THE DEVELOPMENT OF FAST DISSOLVING FILMS:[46]

- Solvent Casting Method
- Hot-Melt Extrusion
- Semisolid Casting
- Solid Dispersion Extrusion
- Rolling

SOLVENT CASTING METHOD

In this method of solvent casting the water -soluble polymers are first dissolved in water at a speed of 1,000 rpm and heated to a maximum of 60°c. Each and every other excipient- colors, flavouring, Sweetener, etc. is dissolved in its own way. After that, the two solutions are well combined while being stirred at 1,000 rpm. The resulting solution is combined with the API that has been dissolved in an appropriate solvent. By using a hoover, the trapped air is released. After the resultant solution is dried and moulded into a film, it is cut into the required size pieces

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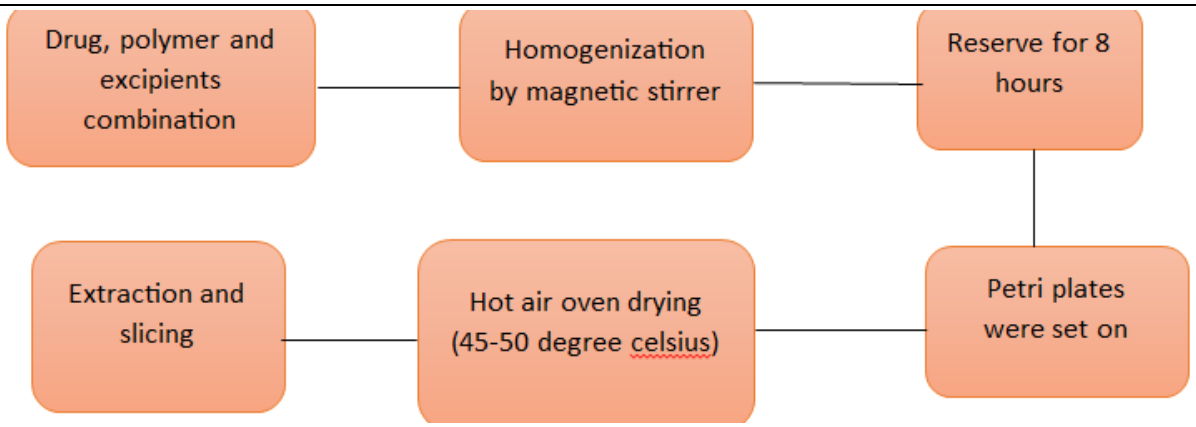

Figure 3: Process of solvent casting method

HOT-MELT EXTRUSION

Extrusion using a hot melt carriers aid in the formation of the initial mass in the hot melt extrusion process. The medication is combined with carriers to create the first bulk, which is then dried and solidified. Next, granular material that has dried is added to the extruder. The temperature of the four zones on the extruder are 800°c (zone1), 1150°c (zone2), 1000°c (zone3), and 650°c (zone4). To process the granules inside the extruder barrel for around 3-4 minutes, the extruder screw speed should be adjusted at 15 rpm. This will ensure that the mass is appropriately liquefied. To create a film, the extrudate (T= 650°c) is then forced into a cylindrical calendar. The following are some advantages of hot melt extrusion: Reduced number of operating units, less product waste, potential for expansion, an anhydrous procedure, lack of organic solvents, shorter drug carrier mix residence time and temperature, and improved content homogeneity are among the benefits.[47]

SEMISOLID CASTING

Casting that is semi-solid this approach is typically chosen when a polymer that is acid insoluble is used as a film constituent. First, water is used to dissolve the water -soluble polymers. The resulting solution is mixed with the separately generated acid-insoluble polymer solution. The two solutions are correctly combined. following the mixing of the two solutions, the proper quantity of plasticizer is added to the resultant final solution in order to get the mass of the gel. Lastly, the gel mass is cast onto the films or ribbons using heat-controlled drums. The film should have a thickness of between 0.015 and 0.05. The acid insoluble polymer and film-forming polymer should have a 1:4 ratio. Cellulose acetate butyrate and cellulose acetate phthalate are two examples of acid-insoluble polymers.

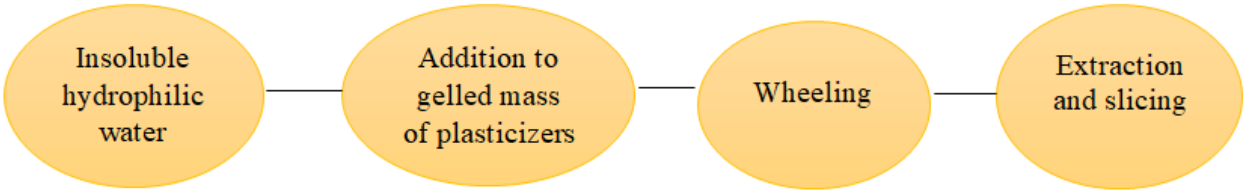

Figure 4: Process of semisolid casting method

SOLID DISPERSION EXTRUSION

A Solid dispersion when amorphous hydrophilic polymers are present and one or more active substances are dispersed in an inert carrier in a solid form, this is referred to as solid dispersion. using this process, medications are dissolved in appropriate solvents and then mixed into the polyethylene glycol melt at temperature lower than 70°c. Dies are then used to eventually shape the solid dispersion into the films.[48]

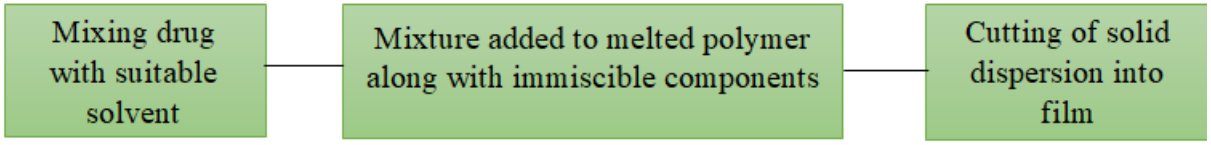

Figure 5: Process of solid Dispersion Extrusion method

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ROLLING

Rolling method: First, foil packaging, polar dissolvable polymers, and extra pharmaceuticals are combined to create a pre-blend. Add the right amount of medication to the pre-blend. The drug is prepared in advance to form a steady grid. The roller accommodates the gathered mixture.[45] A roller assist is used to shape and withdrawn the film. After that, wet film is dried using controlled base drying. The movie is split into the appropriate sizes and categories. It is recommended that the drum roll with distinct rheological properties.[49]

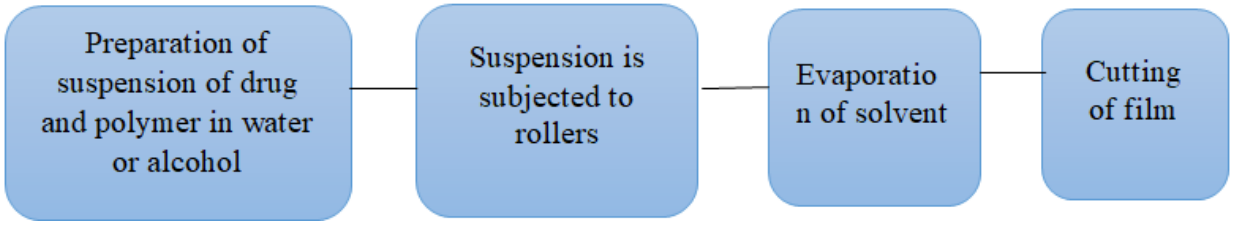

Figure 6: Process of Rolling method

EVALUATION OF ODFs [50-53]

1. **Visual Inspection:** Consistency, quality, and hue of the produced ocular examinations of the film conducted.
2. **Thickness:** Digital Vernier Callipers that have been calibrated or a micrometer screw guage are used to measure the thickness of film. The thickness of the film needs to be measured at five separate points- four at the corners and one in the middle. This is because the uniformity of the film thickness directly affects how accurately the dose is distributed across the film.
3. **Weight Variation:** Every batch of mouth dissolving film had three films measuring 2×2 cm2, which were weighed on an electronic balance to determine the average weight and standard deviation.
4. **Drug Content**: A random sample of drug ODF was used to determine the total amount of drug in each film. The medication analysis was done with a UV spectrophotometric approach. Drug content is limited to 85-115%.
5. **Folding endurance:** This attribute contributes to a film's brittleness. The technique utilized to ascertain the endurance value involves repeatedly folding the film specimen, measuring 2 by 2 cm 2, at the same location until it breaks or a visible crack appears. The computed folding endurance value is the number of times the film can be folded without breaking or showing any visible cracks.
6. **Surface pH test**: The oral mucosa may have adverse effects from the quick dissolving strip's surface pH, so it's important to analyse the film's surface pH. The film's surface pH should be 7 or very nearly neutral. A mixed pH electrode can be used for this. The pH of the oral fil was determined by slightly moistening the OS with water and placing an electrode against its surface. At least six films of each formulation should be studied so that the mean ± SD can be determined.
7. **In -vitro disintegration test:** The point at which an oral film begins to disintegrate when it comes into contact with water is known as the disintegration time or vomit. The disintegration time of a fast- dissolving film should be between five and thirty seconds. Ten milliliters of distilled water were poured in a glass petri dish along with the film size (2×2 cm 2) needed for dosage administration. Every ten seconds, the content of the petri dish were gently swirled until the film began to break. The duration needed for the film to shatter was identified as the in-vitro disintegration period.
8. **In-vitro dissolution studies:** A 2×2 cm2 film was put in a container with 50 cc of Ph 6.8 phosphate buffer that was kept at 37± 0.5°c and 50 rpm stirring speed using a magnetic stirrer. At regular intervals of 0.5,1,1.5,2,2.5,3,4,5 minutes, samples are removed. After being filtered via 0.45 Whatman filter paper, the samples were measured spectrophotometrically at 260 nm. It was determined what proportion of drug was released from each film. For every formulation, graphs showing the percentage of drug release versus time were drawn.

III. CONCLUSION

The current review demonstrates that one of the cutting-edge methods in the pharmaceutical sciences is the use of oral fast dissolving films. Compared to traditional dosage forms, they have better acceptance and patient compliance, no chocking danger, and superior safety and efficacy. The primary motivation behind the development of ODFs was to address the challenge that patients with dysphagia who are pediatric, geriatric, or

psychiatric face when swallowing traditional oral dose forms. ODFs are currently widely accessible for a variety of conditions, including pain, allergies, hypertension, and acidity. One of these dosage forms main benefits is that it can be administered without the requirement for water, which satisfies the need of the target audience who prefer convenience in medication administration. Additionally, because it avoids the hepatic metabolism, the therapeutic response is improved.

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